MEDICAL LIBRARY

Vol. 26 AUGUST, 1949 No. 2

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

EDITORS

ALTON OCHSNER, New Orleans OWEN H. WANGENSTEEN, Minneapolis

ASSOCIATE EDITORS

ALFRED BLALOCK, Baltimore I. S. RAVDIN, Philadelphia

Original Communications

Acute Pancreatitis: Pathways of Enzymes Into the Blood Stream. John M. Howard, M.D., A. Krehl Smith, M.D., and J. Joseph Peters, M.D., Philadelphia, Pa. ---------- 161

Cleft Left Upper Lobes and the Split Anterior Bronchus. Edward A. Boyden, Ph.D., Minneapolis, Minn. ---------- 167

Experimental Tendon Repair Within the Flexor Tunnels: Use of Polyethylene Tubes for Improvement of Functional Results in the Dog. Richard I. Gonzalez, M.D., Denver, Colo. ---------- 181

Hemipelvectomy. Mark M. Ravitch, M.D., Baltimore, Md. ---------- 199

Sulfamethazine in the Treatment of Urinary Infections Due to Gram-Negative Bacilli. Alexander M. Rutenburg, M.D., and Fritz B. Schweinburg, M.D., Boston, Mass. ---------- 215

Meconium Peritonitis. J. Richmond Low, M.D., Princeton, W. Va., George Cooper, Jr., M.D., and Lewis Cosby, Jr., M.D., Charlottesville, Va. ---------- 223

(Contents continued on inside back cover)

Published by THE C. V. MOSBY COMPANY, St. Louis, U. S. A.

Copyright 1949 By The C. V. Mosby Company

SURGERY

ADVISORY COUNCIL

DONALD C. BALFOUR, Rochester, Minn.
VILRAY P. BLAIR, St. Louis
BARNEY BROOKS, Nashville
WILLIAM E. GALLIE, Toronto
EVARTS A. GRAHAM, St. Louis
HOWARD C. NAFFZIGER, San Francisco
HARVEY B. STONE, Baltimore
ALLEN O. WHIPPLE, New York City

EDITORIAL BOARD

FREDERICK A. COLLER, Ann Arbor
EDWARD D. CHURCHILL, Boston
VERNON C. DAVID, Chicago
LESTER R. DRAGSTEDT, Chicago
RALPH K. GHORMLEY, Rochester, Minn.
SAMUEL C. HARVEY, New Haven
FRANK HINMAN, San Francisco
EMILE F. HOLMAN, San Francisco
EDWIN P. LEHMAN, University, Va.
FRANK L. MELENEY, New York City
JOHN J. MORTON, Rochester, N. Y.
THOMAS G. ORR, Kansas City, Kan.
GEORGE T. PACK, New York, N. Y.
WILDER G. PENFIELD, Montreal
WILLIAM F. RIENHOFF, JR., Baltimore

COMMITTEE ON PUBLICATIONS

Arthur W. Allen
Boston, Mass.

Claude S. Beck
Cleveland, Ohio.

Elexious T. Bell
Minneapolis, Minn.

Isaac A. Bigger
Richmond, Va.

Albert C. Broders
Rochester, Minn.

J. Barrett Brown
St. Louis, Mo.

Alexander Brunschwig
New York, N. Y.

Louis A. Buie
Rochester, Minn.

Warren H. Cole
Chicago, Ill.

C. D. Creevy
Minneapolis, Minn.

George M. Curtis
Columbus, Ohio

M. De Bakey
Houston, Texas

William J. Dieckmann
Chicago, Ill.

Daniel C. Elkin
Atlanta, Ga.

Willis D. Gatch
Indianapolis, Ind.

Charles F. Geschickter
Baltimore, Md.

J. Mason Hundley, Jr.
Baltimore, Md.

Andrew C. Ivy
Chicago, Ill.

Dennis E. Jackson
Cincinnati, Ohio

J. Albert Key
St. Louis, Mo.

Chauncey Leake
Galveston, Texas

Francis E. LeJeune
New Orleans, La.

Harold I. Lillie
Rochester, Minn.

John S. Lundy
Rochester, Minn.

Frank C. Mann
Rochester, Minn.

Charles W. Mayo
Rochester, Minn.

Robert L. Payne
Norfolk, Va.

Leo G. Rigler
Minneapolis, Minn.

Ernest Sachs
St. Louis, Mo.

Arthur M. Shipley
Baltimore, Md.

Albert O. Singleton
Galveston, Texas

Maurice B. Visscher
Minneapolis, Minn.

Ralph M. Waters
Madison, Wis.

James C. White
Boston, Mass.

Philip D. Wilson
New York, N. Y.

John A. Wolfer
Chicago, Ill.

Vol. 26, No. 2, August, 1949. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $10.00 a year; Canada and foreign, $11.00. Entered as Second-Class Matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in U. S. A.

SURGERY

VOL. 26 AUGUST, 1949 No. 2

Original Communications

ACUTE PANCREATITIS: PATHWAYS OF ENZYMES INTO THE BLOOD STREAM

JOHN M. HOWARD, M.D., A. KREHL SMITH, M.D., AND J. JOSEPH PETERS, M.D.,
PHILADELPHIA, PA.

(From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania)

ONE of the problems of the pathologic physiology of acute pancreatitis is to explain the rise in serum enzymes which accompanies it and to determine whether this elevation has itself any significant clinical effects.

In man the pancreas and the major salivary glands are known to contain and to secrete into the gastrointestinal tract large amounts of the enzyme, amylase. Injury to one of these organs, particularly the pancreas, in the form of acute external trauma or acute inflammation is associated with a rise in the concentration of amylase in the blood stream.

Indirect evidence is already at hand, pointing to the damaged pancreas as the source of the additional amylase and absorption into the pancreatic venous blood as the most important route of dissemination. Popper and Necheles[1] cannulated the thoracic duct of the dog and collected the lymph for amylase determination. They then traumatized the pancreas. With the lymph exteriorized, the blood concentration rapidly increased. Furthermore, the lymph amylase collected was small in total amount although concentrated. They also found that ligation of the portal vein delayed or prevented the rise in concentration of the amylase in the peripheral blood. That the rise of amylase in the serum is due chiefly to lymphatic absorption is therefore unlikely. The rise in concentration of serum amylase must then be due chiefly to the absorption of the enzyme directly into the blood stream from the damaged pancreas or it must be absorbed indirectly after excretion into the intestinal tract. Introduction of large amounts of amylase into the gastrointestinal tract has not been associated with any rise in serum amylase.[2]

This study has been undertaken to show directly whether or not the injured pancreas is the source of the additional serum amylase and, if so, by what route the additional enzyme reaches the serum.

EXPERIMENTAL

Ten healthy dogs were used as the experimental animals. The dog was chosen because his salivary glands do not secrete amylase,[2] and therefore one variable was eliminated. The experiment was designed to produce two somewhat comparable episodes of acute pancreatitis in each dog within a space of

Received for publication, Feb. 3, 1949.

	CONTROL STUDIES BEFORE AND AFTER ANESTHESIA			MINUTES AFTER PANCREATIC TRAUMA					
						5	10	15	20	30
Pancreatic vein	–	Anesthesia ↑	481	486	Ligation of Pancreatic Ducts—Production of Pancreatitis, 1st exper. ↓	518	602	831	1116	1602
Pancreatic artery	–		502	–		–	–	–	–	–
Aorta	–		506	507		513	524	561	592	639
Femoral vein	501		504	–		–	–	–	–	642
Femoral artery	506		501	–		–	–	–	–	644
Urines	Neg.		–	–		–	–	–	–	Present
Pancreatic vein	–		372	380		488	617	1143	1827	2661
Pancreatic artery	–		393	–		–	–	–	–	725
Aorta	–		390	389		390	437	501	644	719
Femoral vein	400		399	–		–	–	–	–	728
Femoral artery	394		395	–		–	–	–	–	721
Urine	Neg.		–	–		–	–	–	–	Present
Pancreatic vein	–		566	561		784	–	1212	1660	2192
Pancreatic artery	–		580	–		–	–	–	–	–
Aorta	–		580	589		617	632	699	751	771
Femoral vein	579		582	–		–	–	–	–	785
Femoral artery	576		582	–		–	–	–	–	–
Urine	Neg.		–	–		–	–	–	–	Neg.
Pancreatic vein	–		392	415		492	764	–	1213	1682
Pancreatic artery	–		414	–		–	–	–	510	–
Aorta	–		416	412		429	466	–	503	524
Femoral vein	426		408	–		–	–	–	–	522
Femoral artery	427		418	–		–	–	–	–	531
Urine	Neg.		–	–		–	–	–	–	Present
Pancreatic vein	–		531	528		660	811	923	983	1115
Pancreatic artery	–		543	–		–	–	–	–	–
Aorta	–		546	544		570	600	621	632	651
Femoral vein	550		546	–		–	–	–	–	640
Femoral artery	548		542	–		–	–	–	–	644
Urine	Neg.		–	–		–	–	–	–	Present
Pancreatic vein	–		471	471		562	670	759	802	1147
Pancreatic artery	–		474	–		–	–	–	–	691
Aorta	–		476	475		490	508	544	591	682
Femoral vein	481		477	–		–	–	–	–	670
Femoral artery	480		480	–		–	–	–	–	678
Urine	Neg.		–	–		–	–	–	–	Neg.
Pancreatic vein	–		422	425		530	641	728	914	1115
Pancreatic artery	–		431	–		–	–	–	–	–
Aorta	–		431	438		451	478	498	538	601
Femoral vein	420		428	–		–	–	–	–	614
Femoral artery	428		431	–		–	–	–	–	620
Urine	Neg.		–	–		–	–	–	–	Neg.
Pancreatc vein	–		619	615		618	634	656	693	782
Pancreatic artery	–		632	–		–	–	–	–	–
Aorta	–		635	632		634	632	633	641	668
Portal	–		631	629		626	626	634	650	693
Femoral vein	635		636	–		–	–	–	–	660
Femoral artery	631		636	–		–	–	–	–	669
Urine	Neg.		–	–		–	–	–	–	Neg.
Pancreatic vein	–		432	430		448	491	583	696	915
Pancreatic artery	–		461	–		–	–	–	–	–
Aorta	–		458	454		455	463	492	516	629
Portal	–		458	458		455	467	530	589	769
Femoral vein	460		459	–		–	–	–	–	633
Femoral artery	463		455	–		–	–	–	–	636
Urine	Neg.		–	–		–	–	–	–	Neg.
Pancreatic vein	–		573	576		606	693	784	913	1163
Pancreatic artery	–		573	–		–	–	–	–	–
Aorta	–		578	578		582	614	649	735	804
Portal	–		598	579		579	625	663	792	913
Femoral vein	571		575	–		–	–	–	–	813
Femoral artery	573		576	–		–	–	–	–	802
Urine	Neg.		–	–		–	–	–	–	Neg.

*Ligation of thoracic lymph duct was done at completion of this phase of the experiment in all

CONTROL STUDIES BEFORE AND AFTER ANESTHESIA					2.0 c.c. Bile Injected into Pancreatic Duct—Production of Pancreatitis, 2nd exper.						
45	60*				5	10	15	20	30	45	60
–	2571		–	481	515	592	750	918	1224	–	2277
–	895		–	–	–	–	–	–	–	–	–
–	904		–	488	499	531	581	600	645	–	839
–	890		490	495	–	–	588	–	638	–	844
–	–		488	490	–	–	–	–	641	–	–
–	Conc.		–	Neg.	–	–	–	–	Neg.	–	Present
3117	4088		–	416	503	568	681	882	1190	1832	2933
–	–		–	–	–	–	–	–	–	–	–
801	893		–	420	443	467	499	538	606	761	801
–	–		414	416	–	–	489	–	611	–	793
–	–		413	413	–	–	–	–	615	–	–
–	Conc.		Neg.	–	–	–	–	–	Present	–	Present
2604	2888		–	552	690	743	803	977	1343	1882	2490
–	–		–	–	–	–	–	–	–	–	–
799	837		–	556	588	631	669	693	744	790	848
–	–		563	560	–	–	664	–	752	–	839
–	–		559	566	–	–	–	–	–	–	–
	Present		Neg.	–	–	–	–	–	Neg.	–	Present
2914	4267		–	443	493	678	914	1318	2809	3720	4617
–	–		–	–	–	–	–	–	–	–	–
619	863		–	449	461	483	492	544	826	892	951
–	–		452	450	–	–	501	–	830	–	940
–	–		449	414	–	–	–	–	844	–	–
–	Conc.		Neg.	–	–	–	–	–	Present	–	Conc.
1966	3096		–	552	603	718	962	1242	1809	2274	2876
–	1211		–	–	–	–	–	–	–	–	–
803	1219		–	552	584	617	647	736	818	948	1369
–	–		552	554	–	–	642	–	826	–	1348
–	–		558	553	–	–	–	–	813	–	1353
–	Conc.		Neg.	–	–	–	–	–	Conc.	–	Conc.
1632	2138		–	500	597	634	717	839	1422	1793	2683
–	859		–	–	–	–	–	–	770	–	934
703	864		–	513	536	581	598	612	784	816	925
–	871		503	509	–	–	603	–	790	–	936
–	–		499	506	–	–	–	–	781	–	–
–	Trace		Neg.	–	–	–	–	–	–	–	–
1682	2714		–	480	591	621	723	909	1187	1433	2557
–	1001		–	–	–	–	–	–	–	–	1073
827	1011		–	513	515	530	566	581	664	782	1088
–	998		515	518	–	–	560	–	660	–	1093
–	–		516	512	–	–	–	–	649	–	–
–	Conc.		Neg.	–	–	–	–	–	Neg.	–	Conc.
874	1237		–	691	768	813	881	962	1013	1148	1304
–	–		–	–	–	–	–	–	–	–	862
691	764		–	675	693	704	727	781	809	822	856
723	921		–	686	732	748	793	875	934	1048	1091
–	771		680	680	–	–	–	–	815	–	851
–	–		681	675	–	–	–	–	801	–	–
–	Neg.		Neg.	–	–	–	–	–	Neg.	–	Present
1263	2132		–	465	503	629	798	933	1416	1922	2340
–	–		–	–	–	–	–	–	–	–	1319
698	1032		–	455	469	511	543	588	720	912	1338
983	1757		–	455	473	549	581	740	992	1405	1866
–	1017		458	461	–	–	540	–	731	–	1350
–	–		455	459	–	–	–	–	726	–	–
–	Conc.		Neg.	–	–	–	–	–	Neg.	–	Conc.
1440	1908		–	504	613	794	1035	1261	1734	2035	2516
–	–		–	–	–	–	–	–	959	–	1622
930	1115		–	518	561	628	706	793	948	1223	1643
1015	1239		–	514	566	701	887	934	1372	1705	2116
–	1101		518	518	–	–	716	–	960	–	1601
–	–		518	520	–	–	–	–	950	–	–
–	Present		Neg.	–	–	–	–	–	Present	–	Conc.

7 to 10 Days Later

Anesthesia

animals.

two weeks. In the first experiment the pancreatitis was produced by ligation and dissection of the pancreatic ducts. This at the same time assured the complete absence of pancreatic enzymes from the gastrointestinal tract on the occasion of the second induced pancreatitis. The ligation of the thoracic duct after the first experiment was completed excluded the thoracic duct from transporting enzymes at the time of the second experiment. This second pancreatic trauma was produced by injection of bile into the pancreatic ducts of a dog whose pancreatic enzymes thus had access to the body only through the blood stream.

Intravenous sodium pentobarbital, inhalation ether, and 1 per cent procaine locally were selected as anesthetic agents to be used separately. Blood for serum amylase determination was drawn from the femoral vein and artery immediately before and after anesthetization. Urine specimens were obtained at thirty-minute intervals for amylase determination.

Using sterile technique the peritoneal cavity was opened, and blood was taken from the aorta and from small venous and arterial vessels of the pancreas. In three animals the portal blood was similarly studied. An attempt to minimize trauma to the pancreas until these specimens were taken was successful due to the presence of a pancreatic mesentery in the dog. The pancreatic ducts were then ligated at their duodenal orifice necessitating considerable pancreatic trauma. A nonabsorbable ligature was used. Blood specimens were then taken from the aorta and the pancreatic and portal veins at regular intervals for one hour (Table I). At the completion of the abdominal operation the thoracic duct was ligated at its venous outlet in preparation for the subsequent experiment. Again a nonabsorbable ligature was used. Several of the dogs required parenteral glucose and saline as postoperative supportive therapy.

Seven to ten days after the first operation the laparotomy was repeated. Pancreatic trauma was produced this time by the injection of 2.0 c.c. of sterile bile into the pancreatic ducts.

Blood and urine collections were repeated as in the first procedure. The dogs were sacrificed immediately postoperatively, and by careful dissection the occlusion of the pancreatic and thoracic ducts was checked. Specimens of duodenal. ileal, and colonic contents were obtained for amylase analysis.

The amylase concentration of the serum was determined by a modified Somogyi method*[3] and concentration expressed in Somogyi units per 100 c.c. of serum. Each concentration listed represents an average of two or three titrations.

RESULTS

The concentration of amylase in the serum rose rapidly even though the pancreatic and thoracic ducts were obstructed (Fig. 1).

The concentration of serum amylase increased approximately 100 per cent in the femoral vessels within the first hour following the production of a bile-induced pancreatitis. At the same time the concentration of amylase in the serum of the pancreatic veins increased approximately 500 per cent (Fig. 1). An intermediate concentration was found in the portal vein (Fig. 2).

*The modification consisted of incubation of starch with serum for fifteen minutes instead of thirty minutes.

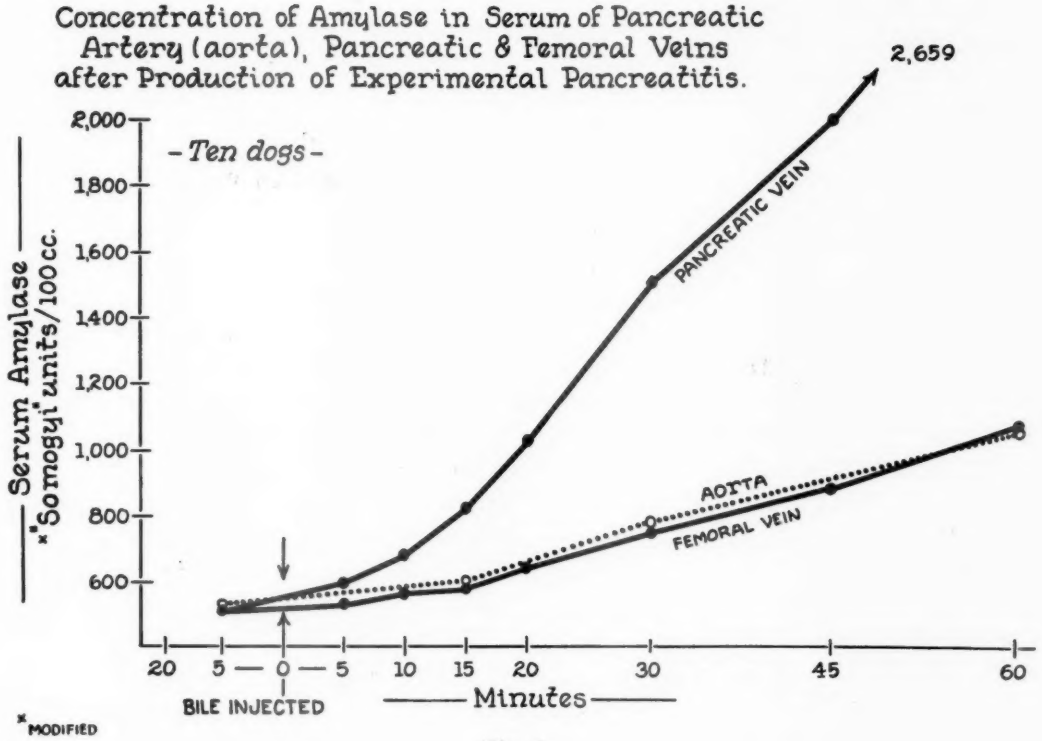

Concentration of Amylase in Serum of Pancreatic Artery (aorta), Pancreatic & Femoral Veins after Production of Experimental Pancreatitis.
2,659
-Ten dogs-
Serum Amylase
*"Somogyi" units/100 cc.
2,000
1,800
1,600
1,400
1,200
1,000
800
600
PANCREATIC VEIN
AORTA
FEMORAL VEIN
20 5 — 0 — 5 10 15 20 30 45 60
BILE INJECTED
Minutes
*MODIFIED

Fig. 1.

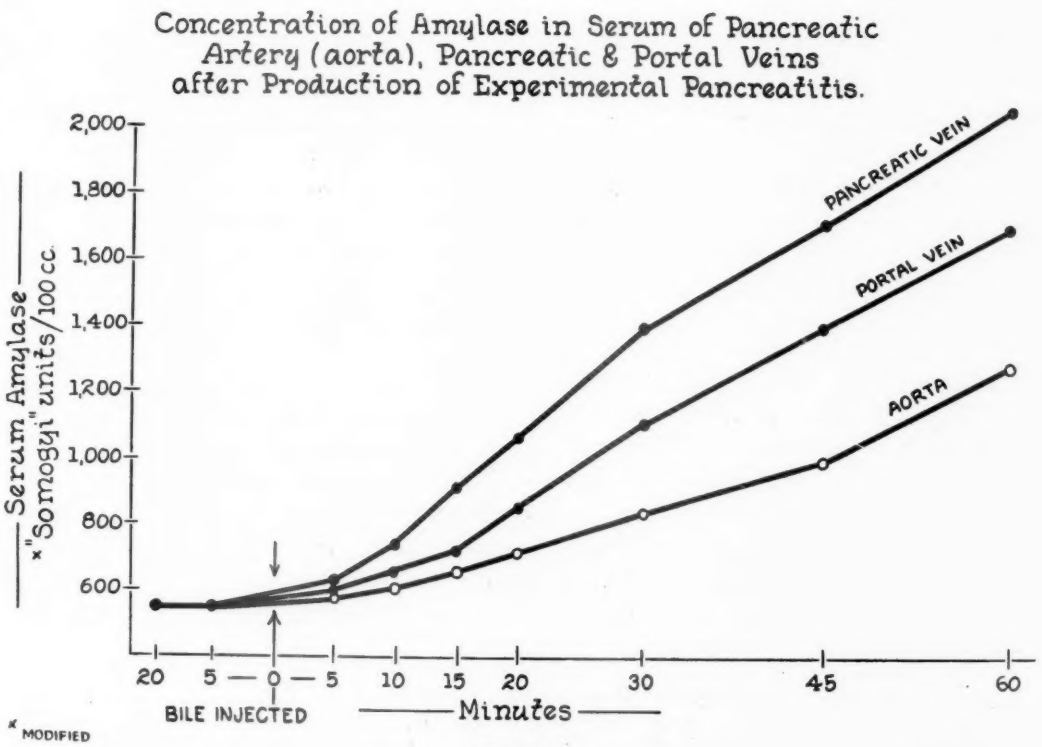

Concentration of Amylase in Serum of Pancreatic Artery (aorta), Pancreatic & Portal Veins after Production of Experimental Pancreatitis.
Serum Amylase
*"Somogyi" units/100 cc.
2,000
1,800
1,600
1,400
1,200
1,000
800
600
PANCREATIC VEIN
PORTAL VEIN
AORTA
20 5 — 0 — 5 10 15 20 30 45 60
BILE INJECTED
Minutes
*MODIFIED

Fig. 2.

Comparison of the concentration of amylase in the aortic blood serum and in blood serum from the veins of the damaged pancreas reveals a much higher concentration in the venous blood serum.

As the serum level rose above an individual threshold, amylase appeared in the urine.

Analysis of the specimens of duodenal, ileal, and colonic contents revealed the absence of amylase seven to ten days after the ligation of the pancreatic ducts. In no instance was there gangrene of the bowel.

DISCUSSION

Comparison of the concentration of amylase in the serum of the artery and vein of the pancreas before trauma reveals values which are almost equal. However, following trauma the concentration in the venous serum of the pancreas is much higher than in the arterial serum. In the absence of amylase in the gastrointestinal tract in the latter experiments, this shows conclusively that the damaged pancreas is the main source of the additional enzyme.

In view of the autopsy findings of obstruction of the thoracic duct and of all of the pancreatic ducts and in the absence of amylase in the saliva and in the intestinal tract, the high concentration of amylase reached in the serum from the pancreatic veins and reflected in that from the femoral vessels must represent release of the enzyme from the traumatized pancreatic cells into the surrounding tissues and absorption directly into the blood stream. As shown by the work of Popper and Necheles,[1] lymphatic absorption plays a secondary role. That the direct blood stream absorption is the route by which amylase enters the serum of the patient with acute pancreatitis has not been proved, but such an inference seems to be a definite possibility.

The very high levels in serum from the pancreatic vein and the portal vein are interesting in comparison with the concentration in serum from femoral vessels as the concentration in the serum of the extremities has been used in experimental and clinical studies. Similarly, trypsin and lipase may be concentrated in the pancreatoportal system following pancreatic trauma. It is possible that one or more of these enzymes is toxic to the liver in high concentration. Indeed, the toxemia of pancreatitis might well be due, in part at least, to such a secondary hepatic damage. This thesis that the enzymes in high concentration may be hepatotoxic has been previously suggested.[1]

SUMMARY AND CONCLUSIONS

Experimental pancreatitis in the dog produces an increase in the concentration of amylase in the serum. That the additional amylase enters the serum from the traumatized pancreas is shown by a much greater concentration of amylase in the serum of the pancreatic vein over that in the serum of the aorta and pancreatic artery. The pathway of the enzyme into the blood stream is chiefly that of absorption directly into the blood stream from the damaged pancreas, a finding which substantiates the conclusion of Popper and Necheles.[1]

REFERENCES

1. Popper, H. L., and Necheles, H.: Pathways of Enzymes Into the Blood in Acute Damage of the Pancreas, Proc. Soc. Exper. Biol & Med. 43: 220, 1940.
2. King, C. E.: Studies on Blood and Urinary Amylase, Am. J. Physiol. 35: 301, 1914.
3. Elman, R.: The Variations of Blood Amylase During Acute Transient Disease of the Pancreas, Ann. Surg. 105: 379, 1937.

CLEFT LEFT UPPER LOBES AND THE SPLIT ANTERIOR BRONCHUS

EDWARD A. BOYDEN, PH.D., MINNEAPOLIS, MINN.

(From the Department of Anatomy, University of Minnesota)

FOR nearly a century anatomists and pathologists have been aware of the fact that not infrequently the right lung may be divided into four lobes and the left lung into three—this quite apart from such bizarre anomalies as the lobe of the azygos vein, the cardiac lobe, and other variants classified and elaborated upon in the recent article by Foster-Carter (1946). Thus in Cruveilhier's *Traité* of 1865, there was a whole page of figures, to be copied the next year in Henle's *Handbuch*. But apparently no attempt to analyze the extra lobe of the left lung was made until 1893 when Bowles presented a case of four right and three left lobes at a meeting of the Anatomical Society of Great Britain and Ireland. Fortunately, the pathologist of Brompton Hospital was present, and the Secretary recorded that after Bowles presented the idea that both lungs had two lower lobes, since the upper left must correspond to the right middle (according to Aeby), "Dr. Ewart regarded the additional lobe in the left lung as derived from the upper lobe and as representing a middle lobe." William Ewart knew what he was talking about, having a more profound knowledge of the bronchial "districts" than any contemporary investigator.

Subsequently, Dévé (1900) found three cases of middle left lobe in 180 infant lungs. On the ground that the supernumerary fissure was horizontal he correctly concluded that the extra lobe corresponded to the middle lobe of the right lung and further, his Fig. 2 (reproduced as Fig. 42 of Brock's monograph, 1944) indicated that the fissure separated the lingular segments (B^4 and B^5) from the remainder of the upper lobe. He was incorrect, however, in assuming that Bowles' case was not that of a middle lobe merely because the fissure was oblique.

A third of a century later the brilliant young thoracic surgeon, Nelson, not long before his untimely death, postulated that the occasional presence of true left middle lobe, plus the occasional occurrence of transverse fissures across the lower lobes (separating Dévé's "dorsal" lobes from the basal segments) afforded strong evidence that each lung really consists of four primary divisions, a broad generalization which has received widespread acceptance.

However, except for the one specimen figured by Dévé, no one seems to have recorded the bronchial content of such middle lobes. The matter was brought to my attention by the finding of eight left upper lobes, cleft in four different ways, in the last fifty dissected specimens. (In the first fifty, analyzed by Boyden and Hartmann, 1946, no prominent extra incisures had been

Aided by grants from the Medical Research Funds of the Graduate School.
Received for publication, Jan. 15, 1949.

encountered.) Curiously enough, no two of these eight specimens were exactly alike (Plate 2 and Fig. 3). Accordingly, it seemed desirable to analyze their bronchial content, but soon it became apparent that a more accurate determination of the normal limits of segments than was previously available would have to be made. With this in mind the fifty specimens of Boyden and Hartmann were re-examined, together with the second fifty recently made available.† A description of the cleft lobes must thus be prefaced by a discussion of the varying limits of the segments, particularly those of the anterior segment.

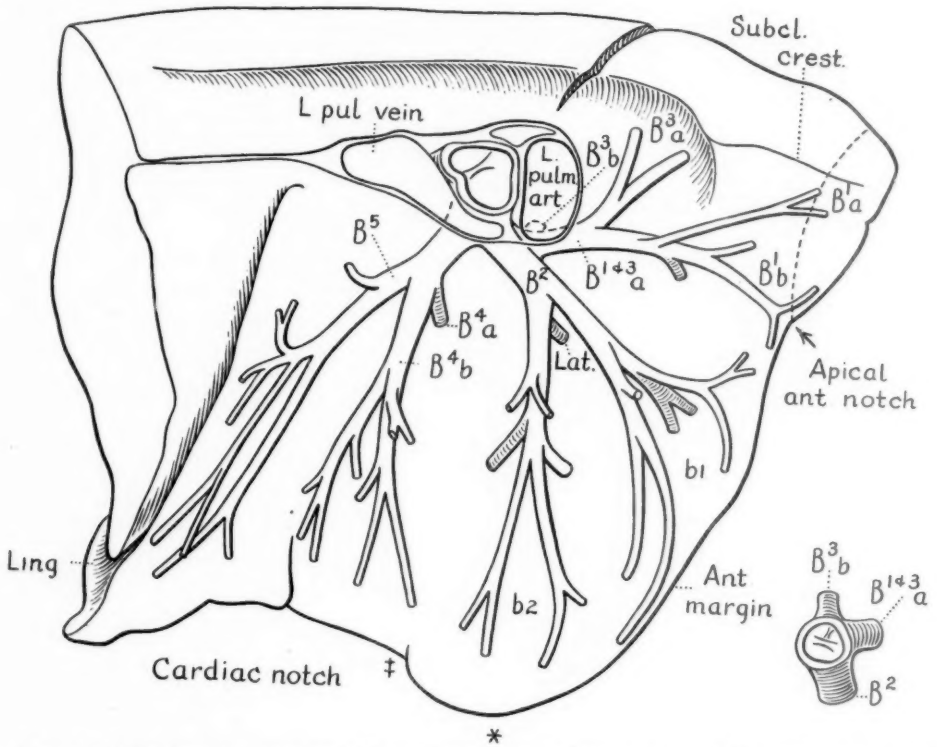


Fig. 1.—Specimen 58, illustrating the bifurcate pattern of the left upper lobe (73 per cent) and the prevailing pattern (62 per cent) in respect to the relations of apical and anterior bronchi. *Upper division:* B^1a and B^1b, apical and anterior rami of apical bronchus (B^1); B^3a and B^3b, apical and posterior rami of posterior bronchus (B^3); B^2b1, B^2b2, anterior rami of anterior bronchus, B^2 (B^2a, the clinically important posterior ramus, is absent in this specimen). *Lower division:* B^4a and B^4b, posterior and anterior rami of superior lingular bronchus; B^5, inferior lingular bronchus. Note that the anterior segment extends from the apical-anterior notch to the 1st cardiac notch (‡)—the arrangement in 38 per cent of 100 specimens—and that B^2 and B^1b are independent of each other. *"Angle" of anterior margin.

1. *The Prevailing Bronchial Pattern of the Left Upper Lobe.*—As illustrated in Fig. 1, the prevailing pattern is *bifurcate,* the bronchus subdividing into a superior and an inferior (or lingular) division. This occurs in virtually three-fourths (73 per cent) of 100 specimens.§ In the remaining 27 per cent, the anterior segmental bronchus (B^2) migrates inferiorly, creating a *trifurcate* pattern. In 7 per cent the orifice of B^2 is exactly central (Fig. 11), in 10 per

†The writer is indebted to Dr. Hartmann for having given this new material his critical attention and for authorizing me to state that the subsequent interpretations, which modify a few details of our earlier work, meet with his approval.

§The earlier reported figure, based on the fifty specimens of Boyden and Hartmann (1946), was 74 per cent.

cent it favors the upper division (Fig. 5), and in 10 per cent it favors the lower division (Fig. 6). Usually, the trifurcate pattern is characterized by an accessory anterior bronchus (BX^2) which buds out of the upper division (Figs. 5 and 6), but in the 6 per cent of specimens in which the displaced anterior bronchus forks almost immediately (Fig. 7) no room for the development of an accessory anterior bronchus seems to have been available.

The reason for continuing to designate as B^2 the anterior bronchus that migrates to a new position, while characterizing as BX^2 the one that develops at the proper site, is that the former almost invariably carries the important posterior ramus (B^2a) and is therefore considered to be the main anterior bronchus. This brings us to a consideration of what I have termed the "split anterior bronchus," a concept that was only partially envisaged in the earlier article.

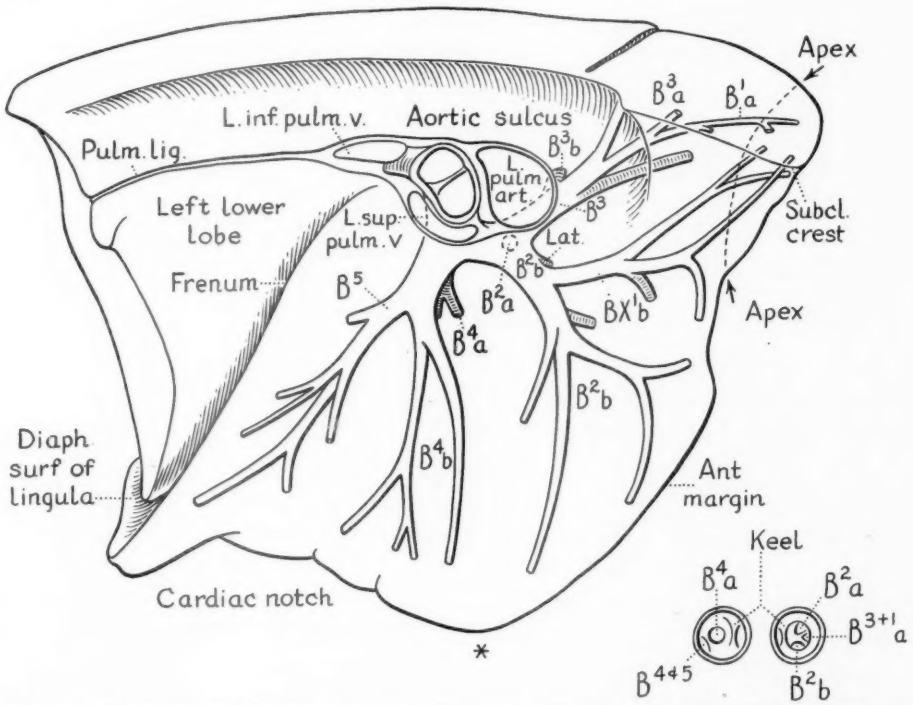


Fig. 2.—Specimen 91, illustrating the bifurcate pattern associated with the displacement of B^1b (11 per cent of specimens). Here, B^1b arises as an accessory branch (BX^1b) of B^2. As a result, the anterior segment now extends from the apex to the angle (*) of the anterior margin. B^2a, the posterior ramus arises independently. (See insert.) In this specimen B^4a arises directly from the lingular stem instead of from B^4, as in Fig. 1 (15 per cent).

2. *The "Split" Anterior Bronchus.*—The tendency for B^2 to be represented by two bronchi of separate origin is pronounced, for an accessory anterior ramus (BX^2) occurs in 33 per cent of 100 specimens (Table I, item 2). Precursors of this pattern may be found in an additional 11 per cent of specimens in which B^2 forks almost as soon as it arises (Fig. 7). From this condition it is only a step to complete separation of the two halves, that is, for two buds to arise embryologically at different places but to grow into the territory usually occupied by a single anterior bronchus.

In all, three types of splitting have been encountered. The first (as recorded by Boyden and Hartmann, 1946) is associated with the trifurcate pattern. In this type, space for the development of an accessory bronchus has been provided by the caudal descent of the main portion of B^2 (as in Fig. 6). This occurs in twenty-one out of twenty-seven trifurcate cases (21 per cent of all specimens); in the remaining six a high and wide-angled forking of the displaced B^2 prevented the development of BX^2 (Fig. 7).

TABLE I. BRONCHIAL DISTRIBUTION TO ANTERIOR ZONE

1. Anterior zone supplied by a single bronchus (B^2)			67%
2. Anterior zone supplied by two separate bronchi (B^2 and BX^2)			33%
(1) B^2 and BX^2 both on upper division of lober bronchus		19%	
(a) Trifurcate pattern: B^2 near center on upper division; BX^2 more distal on upper division (Fig. 5)	9%†		
(b) Bifurcate pattern: both B^2 and BX^2 distal to center but usually close together (Fig. 4)	10%		
(2) B^2 central member of trifburcation, BX^2 distal on upper division			5%†
(3) B^2 and BX^2 on different divisions of lobar bronchus			9%
(a) Trifurcate pattern: B^2 subcentral, on lower division; BX^2 distal, on upper division (Fig. 6)	7%†		
(b) Anomalous bifurcate pattern (ectopic pulmonary artery): B^2 distal on lower division; BX^2 distal on upper division (Fig. 3)	2%		

†Percentages marked with dagger are trifurcate patterns. They total 21 per cent in this table. To these should be added the 6 per cent of specimens having a trifurcate pattern but no BX^2 (Figs. 7 and 11).

A second type, previously figured in the 1946 article (*E*, plate 1) but seen only three times and then without appreciation of its significance, represents an in situ splitting of the anterior bronchus, both components usually remaining close together on the superior division of the left upper lobe stem (Figs. 4 and 10). It occurs in 10 per cent of specimens.† A precursor of this type may be seen in Fig. 13.

The third type is rare and newly recognized. It is associated with the occurrence of an ectopic left pulmonary artery (Fig. 3). In two out of three such anomalous specimens an enlarged inferior division of the left upper lobe bronchus bifurcated into an inferior lingular bronchus (B^5) and an anterior bronchus (B^2), the latter carrying its posterior ramus (B^2a). The superior division bifurcated into B^3 + B^1a and an accessory anterior bronchus (BX^2), from which arose BX^1b (a displaced B^1b).

At this point, one may logically ask on what basis has the bronchus labeled B^2 in Fig. 3 been identified as the main anterior segmental bronchus? Why, for instance, should it not have been called the superior lingular bronchus (B^4)? First, one may state that in the previously figured anomaly of this sort (illustrated by Fig. 6a of the 1946 article), the inferior division virtually broke up into three segmental bronchi, B^2, B^4, and B^5, although B^4 and B^5 had a very short common stem. The specimen shown in Fig. 3 is much like this except that here B^4 is a tributary of B^2. More important, however, is the criterion of distribution. The limits of the territory supplied by B^2 have now been worked out in 100 specimens and in the light of this new information

†Two of these differed from the others in that BX^2 arose more distally.

the ramus labeled B^2, in Fig. 3, may be identified as the principal anterior bronchus.

3. *The Varying Limits of the Anterior Segment.*—If one examines the anterior margin of the left upper lobe (as seen in Fig. 1) three landmarks appear upon which criteria of distribution can be based. The first is an indentation caused by the first rib (see dash line), and may be designated the *apical-anterior notch.* Traced caudally from this point, the anterior margin extends to a region of greatest curvature where it changes its direction markedly. This point may be referred to as the *"angle" of the anterior margin.* It is marked by an asterisk in all figures. From this angle, the margin slopes into

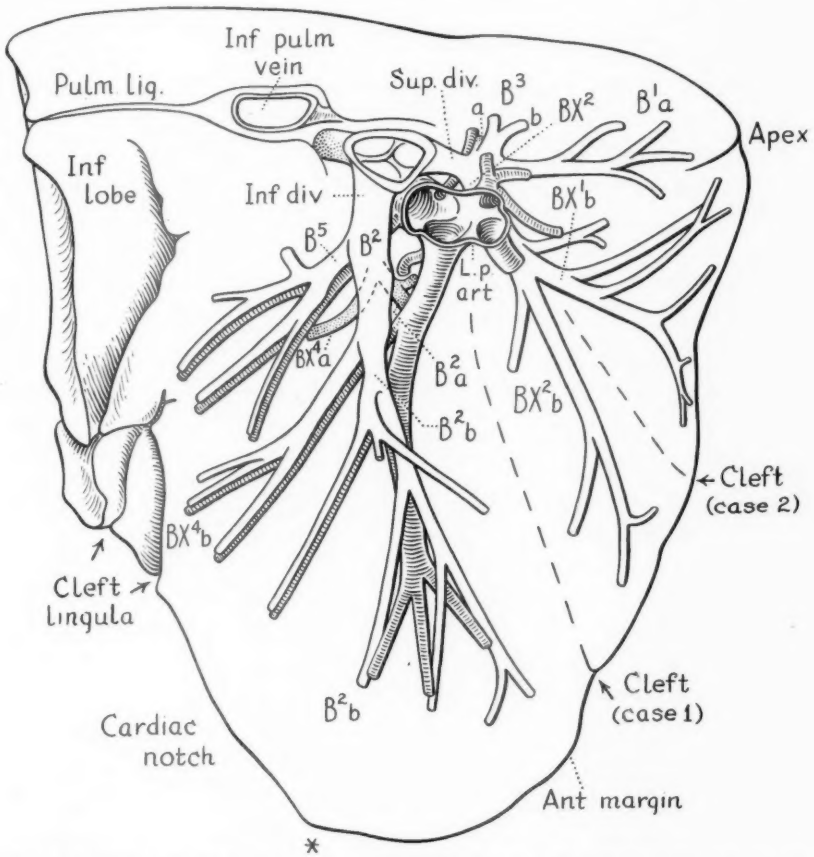


Fig. 3.—Specimen 52, illustrating ectopic position of left pulmonary artery (L. p. art.). Dash lines represent position of a supernumerary cleft in two other specimens. In Case 1 (93) the arrangement of bronchi was virtually the same as in Fig. 3. In Case 2 (59), there was no accessory anterior bronchus (BX^2); as a consequence the oblique cleft separated the apical-anterior segment (B^{1+3}) from the remainder of the lobe, whereas in the first case (93) the cleft occupied the interval between the accessory anterior (BX^2) and the anterior segment proper (B^2). Note the unusual mode of branching of the left bronchus into a modified upper division, a modified lower division, and a lower lobe bronchus. The lower division bifurcates into B^2 and B^3, the former carrying the superior lingular bronchi as accessory rami (BX^4a and BX^4b). Also note supernumerary clefts about the lingula.

the shallow depression known as the cardiac incisure. This is often secondarily indented by small notches varying in number and position. Most constant is the *first notch of the cardiac incisure* (‡, Fig. 1). This first notch of Fig. 1 (or a point correspondingly distant from the angle in other specimens) will be used as the third landmark. Incidentally, this notch was the one re-

ferred to by Churchill and Belsey (1939) as often marking the upper limit of the lingular segments.

Employing these landmarks, it has been ascertained that in 55 per cent of 100 specimens the caudal limit of the anterior segment is the first notch in the cardiac incisure (‡, Fig. 1). This is the prevailing pattern (see Brock, Fig. 49). In another 28 per cent it descends well beyond this point and may even reach as far as the lingula (Fig. 11)†; in another 15 per cent it retreats to the angle of the margin (Fig. 2), and in 2 per cent it even fails to reach the angle.

Conversely, one may say that in 55 per cent of specimens the two lingular segments reach as high up as the first cardiac notch, that in 28 per cent they reach only halfway as far, or less, but that in 15 per cent they extend up to the angle of the margin and, in 2 per cent, even beyond it (see Brock, Fig. 56).

The cranial limit of the anterior segment (Fig. 1) lies at approximately the apical-anterior notch, sometimes a little to one side or the other of it. This is its situation in 56 per cent of specimens. The typical anterior segment may, therefore, be described as extending from the apical-anterior notch to the first cardiac notch. This pattern is realized in 38 per cent of specimens (see Fig. 1; also Fig. 1 of the article by Scannell, 1947, based on gelatin injections of fresh specimens).

The remaining 44 per cent exhibit two major types of variations. The first group comprises the 11 per cent of specimens in which a displaced apical bronchus (BX^1b) originates from the anterior bronchus (Fig. 2; also Scannell's Fig. 2); or from one of its rami (Fig. 7). By virtue of this arrangement the anterior segment becomes greatly enlarged and may even extend from the apex to the first cardiac notch (see Fig. 3 of the article by Scannell).

The second group comprises the 33 per cent of specimens (Table I) in which the main anterior segment (B^2) is reduced to one-half its normal size (Fig. 8), or even to a narrower zone (Figs. 6 and 10), by the development of an accessory anterior bronchus (BX^2). Moreover, since in twenty-seven of these thirty-three cases BX^2 carries a displaced apical bronchus (BX^1b), the accessory anterior segment will usually have a greater length than the anterior proper. (Compare with Fig. 4 of the article by Scannell.)

Of the two extremes, the greatly reduced and the greatly enlarged anterior segment, the latter (that is, B^2 carrying a displaced apical bronchus) is, perhaps, of greater clinical significance since it provides a bronchial pathway by means of which a diseased process in the apex can involve a major portion of the left upper lobe.

4. *The Variable Apical Bronchus* (B^1).—As a corollary to the preceding discussion, attention should be called to the marked tendency of the anterior branch of the apical bronchus (B^1b) to "slide down" onto the anterior bronchus (either B^2 or BX^2). This occurs in 38 per cent of 100 specimens (Table II, item 2). (A comparable displacement of B^1b has been noted in 28 per cent of right upper lobes, Boyden and Scannell, 1948.) It may be compared to the tendency of B^3b (the posterior ramus of the posterior bronchus) to "slide

†Anatomically, the lingula is the "little tongue" that projects onto the diaphragm. The term is incorrectly used to indicate both lingular segments. Usually, the lingula is the termination of B^5, while B^4 reaches the margin between the lingula and the first notch of the cardiac incisure.

down'' the stem of B^3. (Compare positions of B^3b in Figs. 1 and 2.) In fact, B^3b becomes a stem of the second or third order† in 48 per cent of specimens (Boyden and Hartmann, 1946).

Just as B^3b may be easily identified, because it distributes to the upper portion of the interlobar fissure, so B^1b may be easily identified because it points toward the apical-anterior notch; and if it has apical branches these usually approach the apex from the anterior side of the subclavian crest, whereas the apical ramus (B^1a) usually approaches the apex from the posterior side of the crest (Figs. 2 and 4).

TABLE II. ORIGIN OF THE ANTERIOR RAMUS OF THE APICAL BRONCHUS (B^1b)

(1) Anterior ramus (B^1b) a branch of B^1 and therefore entirely independent of the anterior bronchus (B^2)			62%
(a) Bifurcate pattern (B^2 originates on upper division; Fig. 1)	55%		
(b) Trifurcate pattern (B^2 migrates inferiorly, to position between the two divisions; Fig. 9)	7%		
(2) Anterior ramus originates as a displaced ramus (BX^1b) from B^2 (11%), or from BX^2 (27%)			38%
(a) Bifurcate pattern (Figs. 2 and 4)	18%		
(b) Trifurcate pattern (Figs. 7 and 5)	20%		

From the figures in Table II it is obvious that the displacement of B^1b is primarily correlated with the trifurcate pattern, since it occurs in about three-fourths of such specimens, but in only one-fourth of the bifurcate specimens. In further support of this correlation, it can be stated that in 27 per cent of specimens BX^1b, the accessory anterior ramus, is associated with BX^2, the accessory anterior bronchus. Apical and anterior bronchi thus frequently contribute to the formation of a new apical anterior bronchus.

However, one might ask why the bronchus labeled BX^2 in Fig. 5 should not be called B^1b instead of BX^2. The answer is that of thirty-eight specimens having a BX^1b ramus associated with B^2 or BX^2, the B^2 component is larger than the B^1 component in twenty-one of these and that in twelve specimens they are equal, whereas the B^1 component is larger in only five. Accordingly, it seems less confusing to use the term that fits the majority of cases. In addition, there is the progressive series of Figs. 1 to 8 (omitting Fig. 3) which shows the steps by which the anterior ramus of B^1 joins the anterior bronchus (B^2), the way in which that portion of B^2 becomes split off, and how the two halves move apart.

5. *Miscellaneous Observations.*—In concluding this section of the article occasion is taken to present certain supplementary data that were compiled in making dissections of the last fifty left upper lobes.

The posterior ramus (B^2a) of the anterior segment was found to be absent in 30 per cent of the last 50 as against 40 per cent of the first 50, thus making a total of 35 per cent for 100 specimens (that is, an absence of the posterior ramus in one out of every three lungs).

The accessory posterior ramus (BX^2a), arising from the lingular trunk, was found in 14 per cent. The incidence in the first 50 was 10 per cent, thus making a total of 12 per cent for 100 specimens.

†Counting the upper and lower divisions of the upper lobe bronchus as the first order.

The posterior ramus (B^4a) of the superior lingular bronchus arose directly from the lingular division (Fig. 2) instead of from B^4 (Fig. 1) in 18 per cent (as against 12 per cent in the first 50 specimens), thus making a total of 15 per cent in 100 specimens. Adding these to the displaced BX^2a group we find a displaced posterior ramus arising proximally from the lingular stem in 27 per cent of 100 specimens.

The lingular segmental arteries (A^4 and A^5) were found to be wholly posterior in origin in 70 per cent, as previously recorded; they were wholly anterior in 10 per cent as against an earlier 8 per cent, the total for 100 being 9 per cent. They were of mixed origin, occurring on both anterior and posterior surfaces, in 21 per cent.

Three specimens having ectopic left pulmonary arteries were encountered (see Fig. 3) as against none in the first 50 (omitting the one found soon after the first 50 specimens were dissected). Altogether, however, a total of 4 per cent were noted in approximately 100 specimens.

Of special interest are the new observations on the inferior limit of the left upper lobe. It was observed that while in the majority of specimens (56 per cent) the medial end of the lobe was attached to the upper end of the pulmonary ligament in the vicinity of the inferior pulmonary vein—either slightly above it, slightly below it (Fig. 7), or at the vein (Fig. 2)—there was a significantly large number of specimens in which the medial end extended halfway from this point to the diaphragm (8 per cent; for example, Fig. 3), three-fourths of the way (12 per cent; for example, Figs. 4 and 8), or even as far as the diaphragm itself (24 per cent; for example, Figs. 5, 10, and 13).† There was congenital (as contrasted with pathologic) fusion in 24 per cent of the specimens, but in only 4 per cent were bronchi of the upper lobe observed to supply anterior or medial basal segments of the lower lobe (see BX^8a, Fig. 12). In previous dissections of the left lower lobe (Berg, Boyden, and Smith, 1949), two other instances (4 per cent) were noted in which the converse was true, namely, that a basal bronchus (B^7) supplied the fused area of the inferior lingular segment (B^5).

Finally, 8 instances of deeply cleft left upper lobes were found in the last 50 specimens (as against none in the first 50). Soon afterward a doubly cleft specimen was noted (Fig. 15), making a total of 9 cases of "middle lobe" in approximately 100 left lungs.

THE CLEFT LEFT UPPER LOBE

Having established the criteria for recognizing the limits of a given segment, it is now possible to analyze the middle lobes in these anomalous cases. They fall into four categories.

The *first type* (Fig. 10) may be designated a *true middle* (or lingular) *lobe,* since the bronchial elements of the lingular division are complete and the size of superior and inferior lingular segments (B^4 and B^5) is normal. In this respect it resembles Dévé's Fig. 2 (Brock's Fig. 42). Incidentally, this is one of those cases in which the inferior lingular segment is continued to the diaphragm and incompletely fused with the lower lobe (see interlobar fissure).

†It should be recalled that in addition to this abnormal extension of the lower lobe along the pulmonary ligament, the lingula has a diaphragmatic surface in almost all specimens.

Such specimens usually have an extra ramus to supply the new area. Superiorly, the anterior bronchus has split into two components, the upper of which, BX^2, has an apical-anterior distribution. In the second specimen (No. 99), BX^2 has only an anterior distribution.

The *second type* (Figs. 11 and 12) constitutes what may be called a *compressed middle* (or lingular) *lobe.* In Fig. 11, the inferior lingular segment is well developed and the superior is represented by at least the posterior ramus (B^4a). If the ramus labeled B^4b represents the anterior component of B^4 then the lingular segments belong in that 12 per cent of specimens in which B^4a is a branch of the lingular division of the upper lobe bronchus (Boyden and Hartmann, 1946). If B^4b is correctly identified then it is reduced in size, since most of it terminates in the lingula. Compression of the lingular segments seems to have been accomplished by expansion of the anterior segment (B^2) and migration of its bronchus to a central position, this being a true trifurcate pattern.

In Fig. 12, B^4b is rudimentary and B^4a again originates from the lingular stem. In addition, the lingular segments are fused to the lower lobe at the border of the supernumerary fissure, and in this region B^4a sends a substantial ramus to the upper half of the anterior basal segment (BX^8a). Again, the defective size of the lingular segments seems to be associated with hyperdevelopment of the anterior bronchi. The pattern is trifurcate and characterized by splitting of the anterior bronchus. The main stem (B^2, with its posterior ramus, B^2a) has shifted inferiorly, but slightly favors the upper division side (see insert). The accessory bronchus (BX^2) is large and carries BX^1b, the displaced anterior ramus of the apical bronchus.

The *third type,* represented by Figs. 13, 14, and 15, may be called the *enlarged middle* (or lingular) *lobe.* In Fig. 13 the extra lobe has expanded in both directions. Inferiorly, it extends to the diaphragm and is partly fused to the lower lobe. (See interlobar fissure on diaphragmatic surface.) Superiorly, the upper lingular segment (B^4) extends to the angle of the anterior margin and, in addition, it carries a BX^2a, the displaced posterior ramus of the anterior segment. Interestingly enough, this straddles the supernumerary fissure.

A similar termination of B^4 appears in Fig. 14. In fact B^4b reaches so high in the lobe, and B^2 is so much smaller, that one is tempted to consider that B^4 represents a displaced B^2. However, its keel lies 18 mm. below the keel which separates the lingular division from lower lobe bronchus (note anomalous arrangement of orifices) and no other migrating B^2 on the lingular side has had its keel deeper than 9 mm. (most of them being 3 to 6 mm.). For this reason, and to avoid confusing high superior lingular bronchi with the inferiorly displaced anterior bronchi of the trifurcate type, the bronchus in question has been designated B^4. But very likely it represents a transitional form.†

†The point is illustrated by Brock's Fig. 131. In this that author has designated a bronchus as "pectoral" (that is anterior) which apparently originates some 15 mm. below the keel separating upper and lower divisions (assuming that the figure is one-third life-size). We would feel that it is less confusing, and more in accord with the series of figures presented here, to identify Brock's "pectoral" bronchus as the superior lingular (B^4).

EXPLANATION OF PLATE 1

(Drawings rendered for publication by Lawrence B. Benson)

This series of accurate sketches of uncleft specimens is arranged to show the progressive steps in the "splitting" of the anterior segmental bronchus (B^2) and the separation of its two components (indicated by yellow color). It is the basis for interpreting the cleft lobes shown in Plate 2.

Fig. 4.—Specimen 98, illustrating the in situ splitting of the anterior bronchus (10 per cent of specimens). For precursor stage, see B^2, Fig. 13. The lower component carries the clinically important posterior ramus (B^2a) and so retains the designation of the parent bronchus (B^2). The upper component, now called the accessory anterior bronchus (BX^2), carries an accessory apical ramus (BX^1b). Also, in this case, the splitting of B^2 without the downward migration of its main component has permitted an upward expansion of B^4.

Fig. 5.—Specimen 73, illustrating the downward migration of the lower component (B^2) to form a trifurcate pattern. As seen in the insert, the orifice of B^2 is still on the upper division side, the keel separating it from the rest of the upper division lying 4 mm. below the main keel (that is, the one separating upper and lower divisions of the upper lobe bronchus).

Fig. 6.—Specimen 95, illustrating further migration of the lower anterior component (B^2) so that its orifice now lies on the lower division side of the trifurcation. The keel separating it from the lingular bronchi lies 4 mm. below the main keel.

Fig. 7.—Specimen 75. A trifurcate type, favoring the lingular side, as in the previous figure, but here the "splitting" of the anterior bronchus (B^2) is incomplete, consequently no accessory anterior bronchus (BX^2) has arisen. The keel separating B^2 from the lingular stem is 9 mm. below the main keel (that is, the one that separates $B^1a + {}^3$ from the rest of the upper lobe bronchus). If the "splitting" of B^2 had extended into the hilum, then the pattern might have resembled that shown in Fig. 8.

Fig. 8.—Specimen 82, illustrating a case of "split" anterior bronchus (trifurcate pattern), in which the accessory anterior (BX^2) does not carry an apical branch. The keel separating B^2 from the lingular stem lies 6 mm. below the main keel. In this specimen the individual anterior and accessory anterior segments are only one-half as large as the parent segment (Fig. 1). Had the accessory (BX^2) carried a displaced apical branch (BX^1b), as in Fig. 5, then the accessory segment would have been much larger than the anterior proper (B^2). Also note that in this specimen the posterior ramus of the posterior bronchus is displaced, arising as an accessory branch (BX^3b) of BX^2.

Fig. 9.—Specimen 100, a transitional pattern superficially resembling the "split" anterior bronchus type shown in Fig. 8. The complicating factors are the initial direction upward and the high origin of B^4 (the keel between it and B^5 lying only 10 mm. below the main keel that separates upper and lower divisions). However, B^4 does have the characteristic distribution of the superior lingular bronchus and if it were interpreted as a displaced B^2, one would have to say that B^4 is absent.

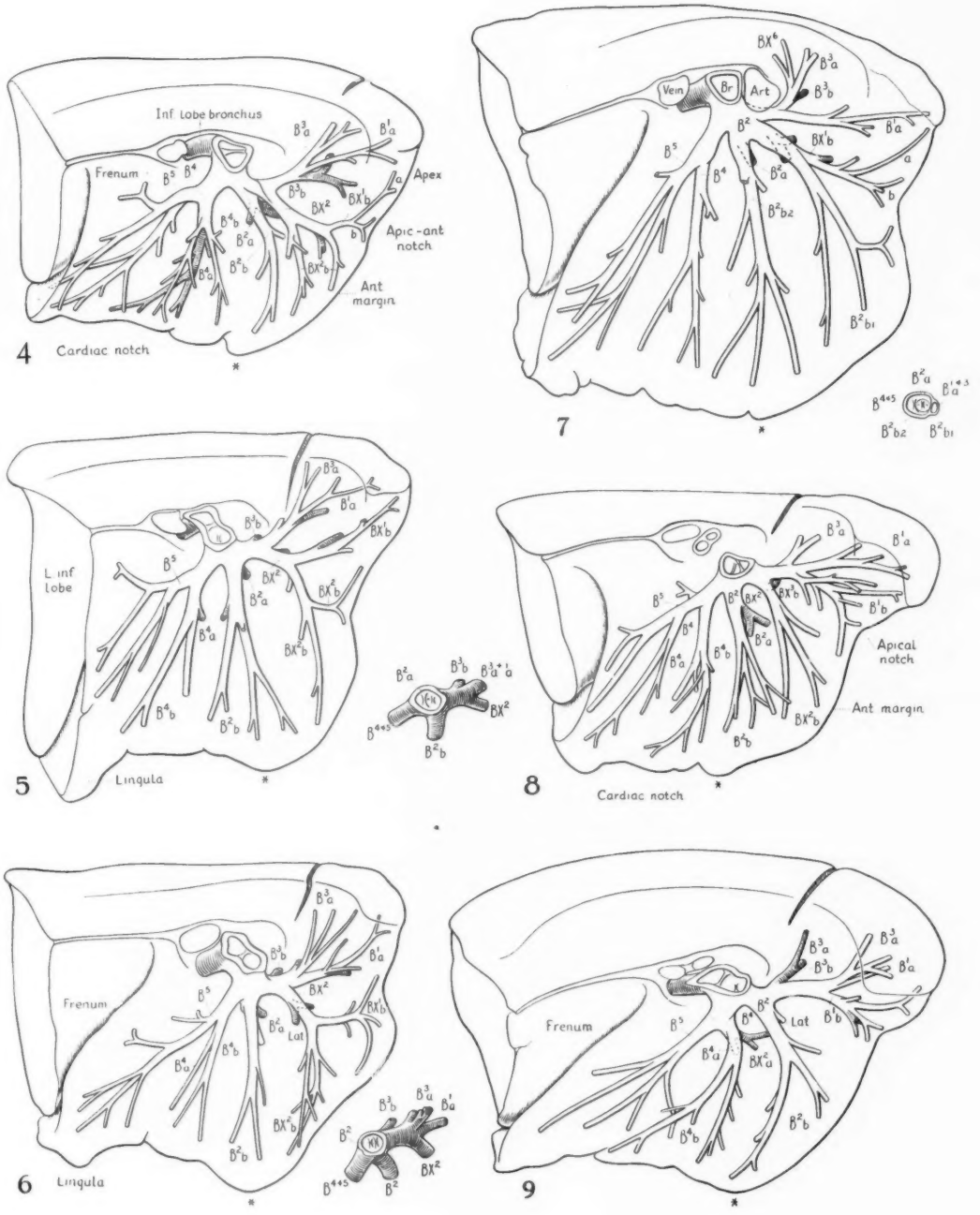
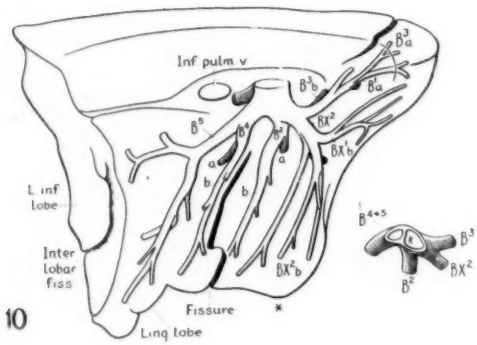
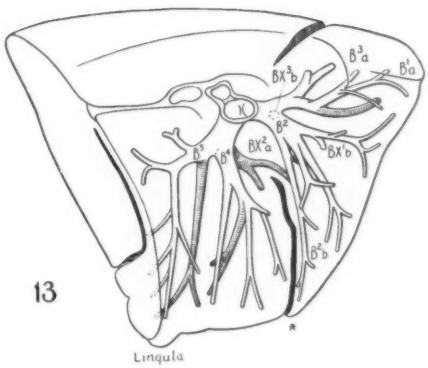
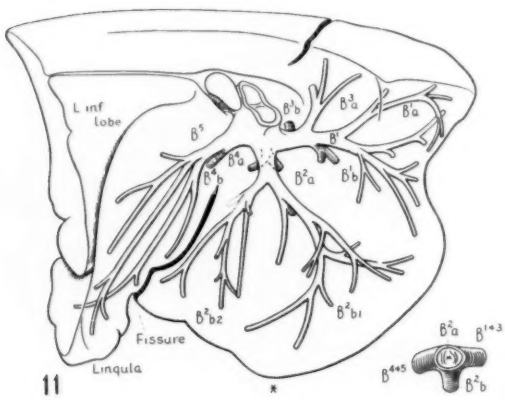
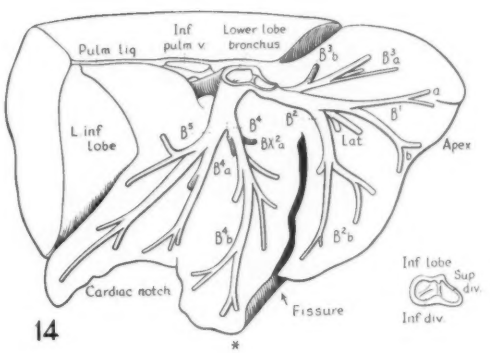

Inf. Lobe bronchus
Frenum
Apex
Apic-ant notch
Ant margin
4 Cardiac notch
Vein
Br
Art
7
L inf lobe
5 Lingula
Apical notch
Ant margin
8 Cardiac notch
Frenum
Lat
6 Lingula
9

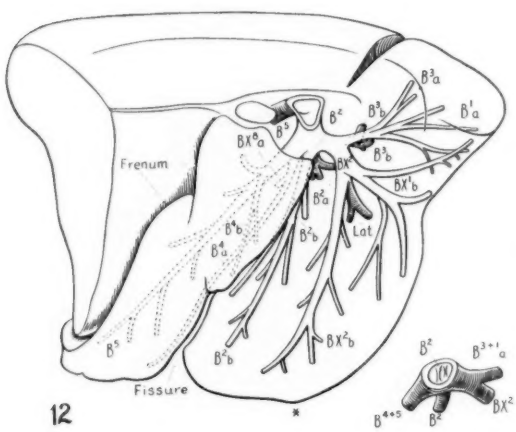
Plate 1.


Inf pulm v.
L inf lobe
Inter lobar fiss.
Fissure
Ling lobe
10


13
Linqula


L inf lobe
Fissure
Linqula
11


Pulm lig
Inf pulm v.
Lower lobe bronchus
L inf lobe
Lat
Apex
Cardiac notch
Fissure
Inf lobe
Sup div.
Inf div.
14


Frenum
Lat
Fissure
12

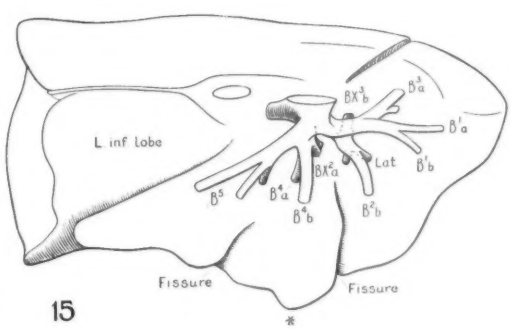

L inf lobe
Lat
Fissure
Fissure
15

Plate 2.

EXPLANATION OF PLATE 2

(Drawings rendered for publication by Lawrence B. Benson)

This series of accurate sketches of cleft left upper lobes is designed to show the varying content of the so-called middle lobe of the left lung and the varying position and direction of the supernumerary fissure. The asterisk (*) marks the angle of the anterior margin, a necessary landmark for interpreting patterns (see Fig. 1). As in Plate 1, the yellow color designates the anterior bronchus or its two separated components, B^2 and BX^2.

Fig. 10.—Specimen 96, illustrating a "true middle" lobe, consisting of normal lingular segments separated from the upper division segments by a nearly horizontal supernumerary fissure. Additional features of this specimen are (1) an in situ splitting of the anterior bronchus (see Fig. 4) and (2) extension of the inferior lingular segment to the diaphragm. The keel separating B^2 and BX^2 lies 9 mm. below the main keel (that which separates upper and lower divisions of the upper lobe bronchus).

Fig. 11.—Specimen 92, illustrating the "compressed lingular" type of middle lobe. The bronchial elements of the lingular segments are present, although arranged in lateral and medial zones, as in the right lung; also B^4a, as occasionally happens (Fig. 2), is a posterior branch of the lingular division rather than of B^4 itself. The striking features of this specimen are the atypical expansion of the anterior segment (B^2), the displacement of its bronchus to form the middle member of a trifurcate upper lobe bronchus, and an oblique supernumerary fissure.

Fig. 12.—Specimen 83, illustrating a still more compressed lingular lobe; one might at first think it was merely an inferior lingular segment segregated by an oblique fissure. (The outline of the extra lobe is shown as it appeared before the position of the bronchi—dash lines— was revealed by dissection.) B^4b is rudimentary and the interlobar surface of the middle lobe is fused to the lower lobe, that portion of the lower lobe being supplied by BX^8a, an accessory branch of B^4a. This type of lobation is again associated with the trifurcate pattern. The orifice of B^2 is on the upper division side, as in Fig. 5, but the direction and distribution of the bronchus are different. Its keel lies 3 mm. below the main keel.

Fig. 13.—Specimen 51, illustrating the "expanded lingular" type of middle lobe. Here, the superior lingular bronchus (B^4) has spread into the territory of B^2 and carries as an accessory ramus (BX^2a), the posterior branch of B^2. Similarly B^2 carries as an accessory ramus (BX^3b) the posterior branch of B^3. In other words this is the reverse of the situation in Fig. 11, where B^2 spread into B^4 territory. The supernumerary fissure is horizontal.

Fig. 14.—Specimen 85, illustrating a transitional type of "expanded" middle lobe. This might be considered to have been formed by cleavage of the space between the two components of a split anterior bronchus (see Fig. 8). In other words, the bronchus designated B^4 could well be a displaced anterior bronchus and B^2 an accessory anterior bronchus, since together they supply the area between the apical-anterior and the first cardiac notch. Furthermore, the one labeled B^5 might be interpreted as having the distribution and elements of the lingular division. However, the lower limit of B^2 is that found in 15 per cent of specimens (see Fig. 4) and the keel separating B^4 from B^5 lies 24 mm. below the keel separating the upper division from the common trunk of the lingular and lower lobe bronchus. For these reasons it seems better to consider the bronchus in question as a high B^4 rather than a greatly displaced B^2.

Fig. 15.—This was a specimen which appeared after the first hundred left lobes had been dissected. Being carcinomatous, its bronchi could not be followed peripherally, but it has two fissures and obviously represents another transitional type. (See discussion under Fig. 15.) The keel separating B^4 and B^5 lies 12 mm. below the main keel.

In Fig. 15, the main supernumerary fissure is like that in Fig. 14, but there is still another fissure which partially separates the two lingular segments. Unfortunately, the lung was so carcinomatous that the bronchi could not be dissected peripherally, but obviously the superior lingular segment (B^4) terminates above the "angle" of the anterior margin. This specimen also represents a transitional pattern, suggesting a split anterior bronchus; but since the keel between B^4 and B^5 is 12 mm. below the keel separating upper and lower divisions, the bronchus which supplies the "angle" has been conservatively designated B^4.†

The *fourth type,* represented by dash lines labeled "case 1" and "case 2," in Fig. 3 may be named the *ectopic arterial type* since the cleft is presumably the result of the ectopic position of the left pulmonary artery. When called to my attention by students, these two specimens had been so completely dissected that adequate drawings of the whole left lung could not be made for publication but the relation of the supernumerary clefts to the bronchi was clear. Accordingly, the position of the clefts was added to a third specimen in which all details were complete.

Obviously the extra lobes in these two specimens are not lingular lobes since each contains the main anterior bronchus (B^2). In "case 1" the cleft developed between the anterior bronchus (B^2) and the accessory anterior bronchus (BX^2). As in Fig. 3, the inferior division of the upper lobe bronchus bifurcated into B^2 and B^5, with B^4 represented by displaced rami which are branches of B^2. Earlier, in this article, reasons for identifying B^2 as such were presented.

The second case differed from the first in that there was no accessory anterior bronchus (BX^2). Accordingly, the cleft separated the apical-posterior trunk (B^{1+3}) from the other bronchi of the lobe (B^2, B^4, and B^5).

It is conceivable, and even probable, that fissures may develop at these sites in the presence of a normally placed pulmonary artery, but at least the two cases listed here provide a fourth example for Foster-Carter's category of abnormal fissures that arise in association with displaced blood vessels—the others being the azygos vein, an abnormal ramus of the thoracic aorta, and the subclavian artery.

In concluding this section it is clear that the so-called "middle lobe" of the left lung, while usually corresponding to the middle lobe of the right lung, is not a consistent structure but may vary considerably in its bronchial content.

SUMMARY

Dissection of fifty left upper lobes in addition to the fifty previously described by Boyden and Hartmann (1946) has revealed certain new features as well as permitting the study of variations to rest upon the broader base of 100 specimens.

†The arteries are of little help in reaching a decision about these transitional cases. In the lobes shown in Figs. 13 and 15, the lingular arteries were of mixed origin—A^4 arising anteriorly and A^5 from the interlobar portion of the pulmonary artery. The same held true in the three specimens of the ectopic type, but in that of Fig. 14 both arteries were interlobar, as in the specimens illustrating the compressed and true types of middle lobe.

The trifurcate pattern of the upper lobe bronchus occurs in 27 per cent, the anterior bronchus (B^2) being exactly the middle member of the tripod in 7 per cent, but favoring upper or lower divisions in the remainder (10 per cent each).

On the basis of more accurate determination of the limits of the anterior segment—which places the inferior (caudal) limit at the first cardiac notch in 55 per cent of 100 specimens, and the superior (cranial) limit at the apical-anterior notch in 56 per cent—it appears that the anterior segment occupies approximately the territory between these two notches in only 38 per cent of specimens. In the remainder the segment spreads upward or downward as a result of two processes.

The first of these is a "splitting" of the anterior bronchus; that is to say, two bronchial buds arise from different sites on the embryonic tree to supply the territory of the anterior segment. The lower one carries the clinically important posterior ramus (B^2a) and therefore retains the designation B^2. The upper one (often the lesser and carrying no posterior ramus) is called the accessory anterior (BX^2), although it originates from the usual site of the anterior bronchus on the upper division stem.

This accessory anterior bronchus (BX^2) occurs in 33 per cent of 100 specimens, and falls into three types. The first (21 per cent) is associated with the trifurcate pattern of the upper lobe bronchus; in these specimens the lower of the two anterior buds arises from a central position. The second type (10 per cent) represents an in situ splitting of B^2, both buds remaining on the upper division. The third type (2 per cent) is rare, being associated with an ectopic pulmonary artery.

A consequence of this splitting of the anterior bronchus is that the anterior segment proper is reduced in size and often thrust caudally out of position, compressing in turn the lingular segments.

A second process, which also changes the size of the anterior segment, is the downward displacement of the anterior ramus of the apical bronchus (B^1b). In 38 per cent, it becomes an accessory anterior bronchus (BX^1b) originating either on the anterior bronchus proper (11 per cent) or on the accessory anterior bronchus (27 per cent). In the former case it greatly expands the size of the anterior segment and is of clinical significance in that it provides a bronchial pathway by means of which a diseased process in the apex may involve a major portion of the left upper lobe. In the latter case it combines with the split-off portion of the anterior segment to form an expanded accessory anterior segment (BX^2) that is larger than the reduced anterior segment proper (B^2).

Applying these new observations to the problem of the cleft upper lobe, it may be stated that the 8 per cent of left lungs exhibiting a "middle lobe" fall into four categories: (1) the true middle (or lingular) lobe (2 per cent); (2) the compressed middle (or lingular) lobe (2 per cent); (3) the expanded middle (or lingular) lobe (2 per cent); (4) the ectopic arterial type (2 per cent) in which the supernumerary fissure lies between B^2 and BX^2 or between B^{1+3} and the remaining bronchi of the upper lobe.

Supplementary observations on a few other points are appended.

The *posterior ramus* of the anterior segment (B^2a) is absent in 35 per cent of 100 specimens.

The accessory posterior ramus (BX^2a, arising from the lingular trunk) occurs in 12 per cent of 100 specimens.

The displaced posterior ramus (B^4a) of the superior lingular bronchus arises from the lingular stem (instead of from the superior lingular bronchus) in 15 per cent of specimens. Adding this to the BX^2 a group, displaced posterior bronchi arise on the lingular stem in 27 per cent of 100 specimens.

The displaced posterior ramus (BX^3b) of the posterior bronchus arises from the anterior bronchus (B^2 or BX^2) in 4 per cent of specimens.

The lingular arteries (A^4 and A^5) are of wholly posterior origin in 72 per cent, of wholly anterior origin in 9 per cent, and of mixed origin in 19 per cent of 100 specimens.

Of special interest are the new observations on the inferior limit of the left upper lobe at the pulmonary ligament. In 56 per cent of 50 specimens it lies at approximately the level of the inferior pulmonary vein (either slightly above, below, or at the vein). In 24 per cent the upper lobe extends to the diaphragm, in 12 per cent three-fourths of the way, and in 8 per cent one-half of the way. In 24 per cent, nearly one-half of these inferiorly extended lobes, there was congenital fusion of upper and lower lobes in the inferior lingular area; in 4 per cent the inferior lingular bronchus (B^5) sent branches into the adjacent basal segments.

REFERENCES

Berg, Roger M., Boyden, Edward A., and Smith, Franklin A.: An Analysis of Variations of the Segmental Bronchi of the Left Lower Lobe of Fifty Dissected, and Ten Injected, Lungs, J. Thoracic Surg. **18**: 216-236, 1949.

Bowles, Dr.: Lung With Four Lobes, Proc. Anat. Soc. Gr. Britain & Ireland, J. Anat. & Physiol. **28**: 271, 1894.

Boyden, Edward A., and Hartmann, J. Francis: An Analysis of Variations in the Bronchopulmonary Segments of the Left Upper Lobes of Fifty Lungs, Am. J. Anat. **79**: 321-360, 1946.

Boyden, Edward A., and Scannell, J. Gordon: An Analysis of Variations in the Bronchovascular Pattern of the Right Upper Lobe of Fifty Lungs, Am. J. Anat. **82**: 27-74, 1948.

Brock, R. C.: The Anatomy of the Bronchial Tree, With Special Reference to the Surgery of Lung Abscess, London, 1946, Oxford University Press. (Also Guy's Hosp. Rep. **92**: 26-37, 1943; **93**: 90-107, 1944.)

Churchill, Edward D., and Belsey, Ronald: Segmental Pneumonectomy in Bronchiectasis, Ann. Surg. **109**: 481-499, 1939.

Cruveilhier, J.: Traité d'anatomie descriptive, ed. 4, Tome II, Splanchnologie, Paris, 1865, P. Asselin.

Dévé, M. F.: Valeur du lobe supérieur du poumon gauche, Bull. et mém. Soc. Anat. **2**: 368-374, 1900.

Foster-Carter, A. F.: Broncho-pulmonary Abnormalities, Brit. J. Tuberc. **40**: 111, 1946. (Also Brompton Hosp. Rep. **16**: 100-127, 1947.)

Henle, J.: Handbuch der Systematischen Anatomie des Menschen, Bd. 2, Eingeweidelehre, Braunschweig, 1866, Friedrich Vieweg u. Sohn.

Nelson, H. P.: The Tracheo-bronchial Lymphatic Glands, J. Anat. **66**: 228-241, 1932.

Idem: Postural Drainage of the Lungs, Brit. Med. J. **2**: 251-255, 1934.

Scannell, J. Gordon: A Study of Variations of the Bronchopulmonary Segments in the Left Upper Lobe, J. Thoracic Surg. **16**: 530-537, 1947.

Scannell, J. Gordon, and Boyden, Edward A.: A Study of Variations of the Bronchopulmonary Segments of the Right Upper Lobe, J. Thoracic Surg. **17**: 232-237, 1948.

EXPERIMENTAL TENDON REPAIR WITHIN THE FLEXOR TUNNELS: USE OF POLYETHYLENE TUBES FOR IMPROVEMENT OF FUNCTIONAL RESULTS IN THE DOG

RICHARD I. GONZALEZ, M.D.,* DENVER, COLO.

(From the Halsted Experimental Surgical Laboratory, Department of Surgery, University of Colorado Medical Center)

PRIMARY tendon repair is a subject of universal interest. The general practitioner as well as the specialized hand surgeon find in it common problems. Both are interested in obtaining good function following repair. Both realize that many factors influence their results: the time interval between accident and repair, the degree of trauma to superficial and deep structures, the degree of contamination at the time of injury, the surgical technique employed, and lastly, yet perhaps most important, the location of the injury. All other things being equal, the degree of functional recovery following primary tendon suture can be predicted from the location of the injury. With clean wounds, early repair, and careful surgical technique, good to excellent functional results usually follow primary tendon repair of the extensors, and also of the flexors if the transection of tendon occurs in the forearm, wrist, proximal palm, or distal inch of the finger. However, if a flexor tendon is severed in the proximal two-thirds of the finger or the distal inch of the palm there is usually minimal return of function. Bunnell[1] calls this the "no man's land" of tendon repair and stated,[2] "Severance of flexor tendons in the proximal segment of a finger and distal inch in the palm is not only the most common injury, but is followed by the poorest results. When the problem of repairing a flexor tendon at this site is solved, the repair of all tendons will be comparatively easy."

It is with this particular problem that we are concerned. The reason for the minimal return of function following primary suture in this region is due to the anatomy of the flexor mechanism in the finger. The flexor profundus, flexor sublimus, and their common synovial sheath are enclosed in a snug-fitting fibrous tunnel in the region overlying the proximal phalanx. If it were not for the lubricating action of the synovial fluid, it is doubtful whether the tendons would be able to move at all in this area. Trauma in this region, which results in even minimal scarring, greatly impairs the gliding mechanism of these closely apposed structures. A major injury, such as laceration of a tendon plus the subsequent trauma of surgical repair, is all too often followed by complete breakdown of the gliding mechanism. In its place immobile adhesions form, binding tendons, sheath, and tunnel into a dense adherent mass. Unfortunately, this is the end result in the majority of cases despite the most careful of atraumatic techniques, and is always the end result when there is any deviation from strict asepsis, careful hemostasis, or gentle handling of tissues.

Other workers besides Bunnell stress the poor prognosis of tendon repair within the osseofibrous tunnels. Cootes[3] stated, "(I) have never heard of a

Received for publication, March 7, 1949.

*Fellow in Experimental Surgery.

case where a flexor tendon divided in its digital sheath has been restored to usefulness by suture." Teece[4] was also quite pessimistic and stated, "I have never seen a successful primary or secondary suture of a flexor tendon when the point of division is actually within the flexor sheath itself." Mouat[5] stated, "(My) twenty-five years' experience in a city in which the local trades predispose to such injuries coincides exactly with that of Teece."

Statistical analyses of functional results following primary suture within the flexor tunnel are hard to find in the literature. One is led to believe that the reason for this is that poor results far outweigh the good ones. However, an exception to this is the very careful analysis by Miller[6] of 300 cases of tendon repair done at the Detroit Receiving Hospital. Thirty-one repairs were done on flexor tendons over the proximal phalanges. Twenty, or 60 per cent, of these repairs resulted in good function (80 per cent return of normal function), eleven, or 40 per cent, resulted in poor or nonfunctioning tendons. A more optimistic outlook was given by Posch,[7] who reported twenty out of twenty-six good to excellent results following primary tendon suture within the flexor sheath. It would be interesting to know how many of those repairs were done within the flexor tunnel, the area in which the poorest results occur.

In summary it appears that primary tendon repair within the flexor tunnel is still the number one problem of tendon surgery.

In the past, the attempts toward the solution of this problem have been made from three directions: (1) perfection of surgical technique in the primary repair; (2) use of new reconstructive methods in secondary procedures; (3) attempts to block the formation of adhesions by wrapping the tendon and excluding the anastomosis from the extra tendon structures by means of organic and inorganic membranes.

The greatest amount of clinical effort has been directed toward the refinement of delicate atraumatic techniques in the primary repair of the tendons. Bunnell,[1, 2] Koch,[8] Mason,[9] and Posch[7] have all contributed to this field. Their results in the flexor tunnel, however, still do not compare with tendon repairs in other regions.

In many cases secondary procedures have been done in the attempt to overcome the bad results of the primary repair. Much experimental and clinical work has been done in this field. The use of the free tendon graft has been successful in some hands.[2, 8] Mayer[10] attempted to construct a new, nonadherent sheath in order to achieve greater function in tendon grafting. Despite these efforts, free tendon grafts become functional only in the best of hands.

The use of membranes in the form of tubes or wrappings around the repaired tendon with the hope of preventing adhesion formation has been advanced by many authors using many different types of membranes. Wilmoth[11] advocated the use of tunica vaginalis. Davis[12] experimented with beef amniotic membrane, beef allantoic membrane, sheets of catgut, beef, cecum, and cellophane. Wheeldon[13] used cellophane in a clinical case. McKee[14] implanted Vitallium tubes about the tendon anastomoses with subsequent removal of the tube. All of these materials plus many more have been tried without outstanding success. In addition, a theoretical objection to the wrapping of tendons

was voiced by Koch,[8] who stated, "The nutrition of the tendon within the finger must come in part from the capillaries of the subcutaneous tissue which overlies it. Blocking off the ingrowth of blood vessels at the line of suture jeopardizes the sound healing of the sutured tendon ends which is the first essential to restoration of function."

Despite the failure of other workers to prevent adhesion formation with their membranes and the possibility that good tendon healing requires the blood supply of the extratendon tissues, we felt that the "block" method offered enough promise for further investigation. In our study we hoped to accomplish three goals: (1) to find a suitable membrane for the "block" technique (one that was inert in body tissue, yet at the same time pliable and workable into tubes of varied length and diameter); (2) to prove experimentally whether or not tendons can heal strongly even though blocked away from the extratendon tissues; and (3) to show experimentally whether or not function following primary tendon repair within the flexor tunnel can be definitely improved by the use of the "block" technique.

METHOD

The first step in the solution of our problems was the development of a well-controlled experimental method. The experimental method must satisfy three criteria: (1) The anatomy of the flexor mechanism of the experimental animal and the human being must be essentially the same; (2) the experiment must be well-controlled; (3) adequate standards and methods for determining union and function of the experimental tendons must be devised.

The dog's flexor mechanism in the forefoot is almost the exact anatomic and functional counterpart of that of the human hand. The profundus and sublimus tendons are enclosed in a synovial sheath both in the palm and the digit. The two tendons with their common sheath are enclosed in a tight fitting osseofibrous tunnel as they pass over the proximal phalanx. The sublimus splits and the profundus passes between the diverging slips at the junction of the proximal and middle phalanx. The middle pulley crosses the sheath and the profundus tendon at the midpoint of the middle phalanx (Fig. 1). All the components found in the human tunnel area (distal palm and proximal phalanx) that would contribute to posttraumatic adherence of the tendons are found in the same area in the dog.

All the slips of the canine flexor digitorum profundus are fused at the wrist. This makes it possible to weave a tension wire with a pull-out loop through the common portion of the tendon and by so doing to relax all the distal slips of the tendon. Thus, the investigator may do primary tendon suture on two or more tendons under exactly similar conditions utilizing one tendon for experiment and one or more tendons for control.

Two of the criteria are hence fulfilled: (1) The anatomy of the dog's flexor mechanism is the counterpart of the human; and (2) the anatomy of the dog provides the ideal situation for well-controlled experiment concerned with the distal slips of the flexor profundus in the foreleg. The establishment of standards for the measurement of union and function will be discussed subsequently.

The first operative problem to consider was the type of tendon suture to use. Bunnell's[1] "suture-at-a-distance" technique was chosen for several reasons. First, it seemed logical that a technique leaving the least nonabsorbable suture material in the tendon would probably lead to minimal reaction and adhesion formation. Second, by placing the tension wire and pull-out loop in the wrist both experimental and control tendons were relaxed with a single maneuver. Third, the clinical results obtained by Bunnell[2] utilizing this technique compared favorably with those utilizing other methods. This method was found to be extremely simple, quick, and completely satisfactory in the 190 experimental primary tendon anastomoses that were done in connection with this project.

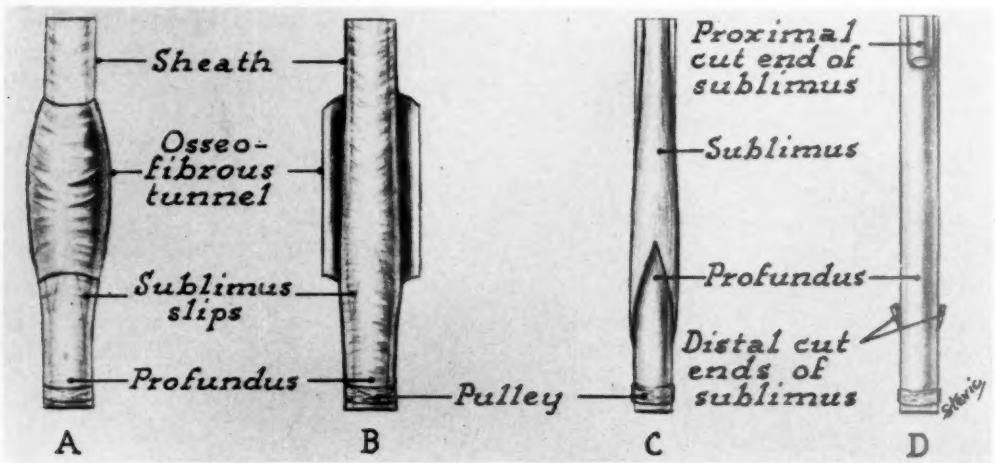


Fig. 1.—Semidiagrammatic drawing of the flexor mechanism of the dog in the digits. Note the similarity of the dog's anatomy in this region to that of the human. (*A*) Superficial dissection showing the osseofibrous tunnel and synovial sheath intact. (*B*) The osseofibrous tunnel has been split and drawn apart. The sheath is still intact. (*C*) The osseofibrous tunnel and sheath have been removed. (*D*) The sublimus has been transected distally at its insertion and proximally at the end of the tunnel. The profunda alone remains.

Mongrel dogs of either sex, weighing between 8 and 26 kilograms were used. Dogs weighing 15 kilograms or more were preferred because of the greater size of their tendons. The dogs, with no preoperative medication, were anesthetized by the intravenous administration of an aqueous solution of sodium nembutal (1 gr. per cubic centimeter) in a dose of 0.44 c.c. per kilogram. Placed on their backs on a dog operating table, the volar surface of the wrist, palm, and the outer aspects of the second (index) and fifth (little) digits were carefully shaved. The foreleg was made bloodless by an Esmarch bandage followed by a rubber tourniquet just above the elbow. The foreleg was fixed to a Mayo stand using a four-foot loop of heavy string running from a clove hitch about the muscular portion of the foreleg around the Mayo stand at right angles, thus immobilizing the foreleg but leaving the wrist, palm, and digits completely free. The shaved area was carefully scrubbed for four minutes with a three per cent aqueous hyamine solution. The germicidal and cleansing properties of this solution have been described by Swan and associates.[15] The operative area was then carefully draped in order to expose the foreleg from the wrist to the toes. A cap of

sterile two inch tubular stockinet was placed over the toes and phalangeal footpads. A longer (one foot) length of two inch stockinet was then placed over the entire exposed foreleg.

The first operative step was the insertion of the tension wire. Over the medial aspect of the wrist, a two inch curved skin incision was made through the stockinet (see Fig. 2). The skin edges were fixed to the cut edges of the stockinet by small Michel skin clips. The underlying superficial structures were isolated and retracted, the common portion of the profundus tendon mobilized and brought into the wound by passing a knife handle beneath it.

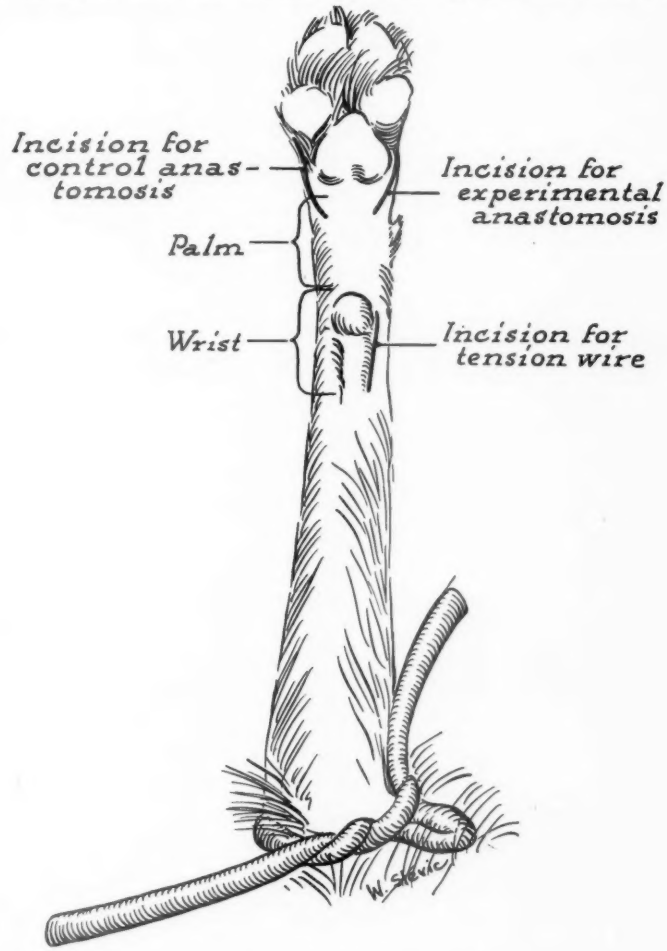


Fig. 2.—Semidiagrammatic sketch indicating the location of the three skin incisions. The *Palm* and *Wrist* indicate the regions in the dog which correspond to similar regions in the human being.

A No. 32 stainless steel tension wire with a proximal pull-out loop was woven through the common portion of the tendon after the method of Bunnell.[2] The proximal pull-out loop and distal ends of the tension wire were brought through the skin through buttons, fixed with shot, and tied over the shot. Fairly strong traction was exerted on the tension wire in order to relax completely the distal portions of the tendon.

The wrist incision was covered with sterile gauze to preclude contamination until the end of the procedure when all the skin incisions were closed. The scene of operation was then shifted to the digits.

A new incision was made over the lateral aspect of the second (index) digit (see Fig. 2). The volar surface of the osseofibrous tunnel, and the sheath and pulley distal to it were exposed. The sheath was incised distal to the tunnel but proximal to the middle pulley. The sheath and the volar surface of the tunnel were split longitudinally to the proximal end of the tunnel. The sublimus tendon was excised from the distal insertion of its diverging slips to the proximal end of the fibro-osseous tunnel to eliminate the possibility of its adhering to the suture line.

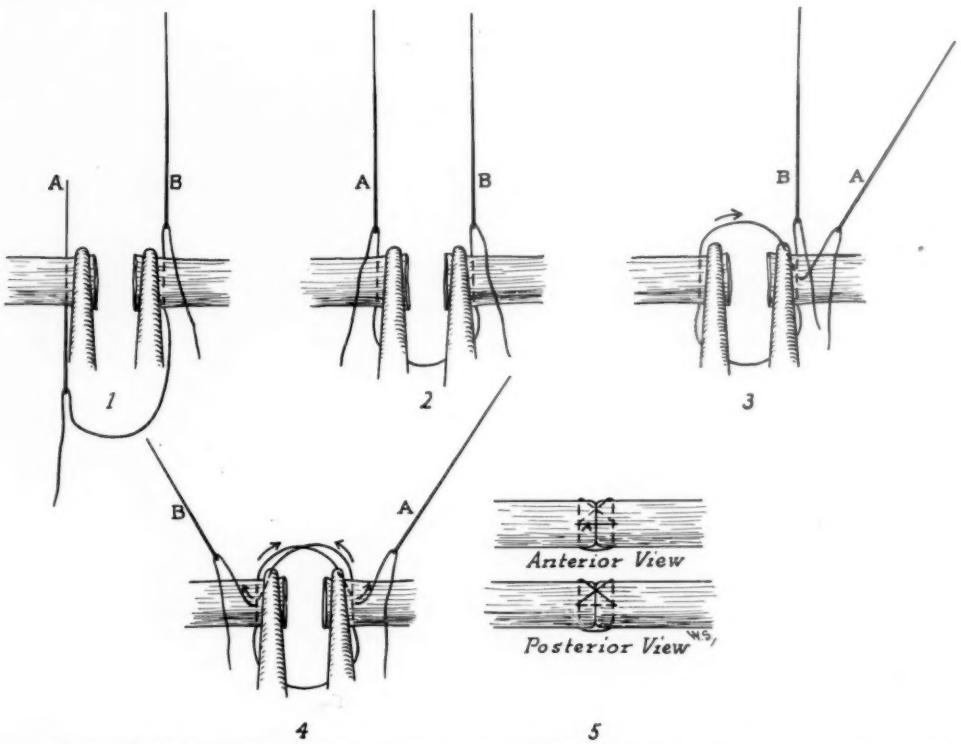


Fig. 3.—Diagrammatic representation of modification of the double right-angle (basket-weave) approximation suture. (*1*) Needle *B* enters distal tendon segment at right angles to its smallest diameter; Needle *A* repeats step through proximal segment. (*2*) Both needles have been pulled through tendon. (*3*) Needle *A* enters distal segment of tendon posteriorly and at right angles to previous suture. (*4*) Needle *B* repeats step through proximal segment. Crushed tendon ends are now carefully cut across behind clamps. (*5*) Suture tightened and tied.

The free-lying, relaxed profundus was cut across with a knife in the middle of the tunnel. The experimental tube was then threaded over either the distal or proximal segment of the tendon. The free tendon ends were grasped with straight mosquito clamps and a single basket-weave suture of 0000 braided silk (Fig. 3) was placed in the tendon ends just behind the clamps. The technique of placing this suture was modified from that of Bunnell[2] in that two needles, one at each end of the suture, were used. By this technique, the twisting tendency of the one needle method was obviated. The tendon ends were then carefully cut across immediately behind the crushed tips of the tendons, held in the

mosquito clamps, and the suture tightened and tied. It was possible to obtain extremely accurate approximation with this method.

After the suture was completed, the experimental tube was brought over the anastomosis. The edge of the tube was anchored to the lateral wall of the tunnel with a single suture of 0000 silk to prevent possible displacement.

For the control procedure, a new skin incision was made over the lateral aspect of the fifth (little) digit, the tunnel opened, the sheath split, the sublimis excised, and the profundus transected. The cut ends were carefully approximated with the same basket-weave suture of 0000 silk. No tube was used around this anastomosis.

The skin clips were then removed and the skin incisions closed with interrupted vertical mattress sutures of 0000 silk. The tourniquet was released and two layers of serially wound sheet wadding were placed about the foreleg, from toes to elbow. Three to four layers of plaster of Paris were then wrapped around the leg. A wide splint of leaded wire screen (½ inch square) was molded about the forearm, and placed between the two outer layers of plaster. After the plaster had dried, the cast was entirely covered with strips of adhesive tape.

Obtaining long periods of immobilization was found to be one of the most difficult technical problems. The dogs found it very easy to chew off ordinary plaster casts. Aluminum splints incorporated within the casts were not successful in preventing the early loss of immobilization. Plastic (Aire-lite) casts were no better. The final system (padded plaster, plus wire screening) was quite successful and these casts stayed on indefinitely. In my experience, dogs would not tolerate unpadded plaster casts and even though such a cast was carefully applied, a high incidence of pressure sores and secondary infections occurred.

After selected periods of immobilization the casts were removed. Tests for strength and function were performed at varying intervals thereafter. For these tests, the dog was anesthetized and placed on his back on the animal operating table. The volar surface of the foreleg was shaved and scrubbed. The foreleg was rendered bloodless and new incisions were made over the fifth and second digits. The new incisions were longer than the original ones in order to mobilize the tendon slips in unoperated areas, that is, beyond the middle pulley distally and in the palm proximally. After the tendon had been freed in these areas, longitudinal traction was applied to the proximal segment of the tendon, and the excursion of the distal segment of the tendon carefully noted. The distal tendon was then transected above the pulley, and traction again applied to the proximal segment of the tendon. If it were possible to withdraw the divided tendon, the gross amount of pull was noted. If it were impossible to withdraw the tendon, it was carefully dissected out. The tendon segments thus removed (by withdrawal or dissection) were then placed in a tensiometer (Fig. 4), in which it was possible to measure in pounds the pull necessary to break the sutured tendons. The tensile strength of the tendon was computed in grams per square millimeter (the cross sectional area of the tendon having been previously determined). It was impossible to break a few of the tendons with this apparatus. The tensile strength of these tendons was reported

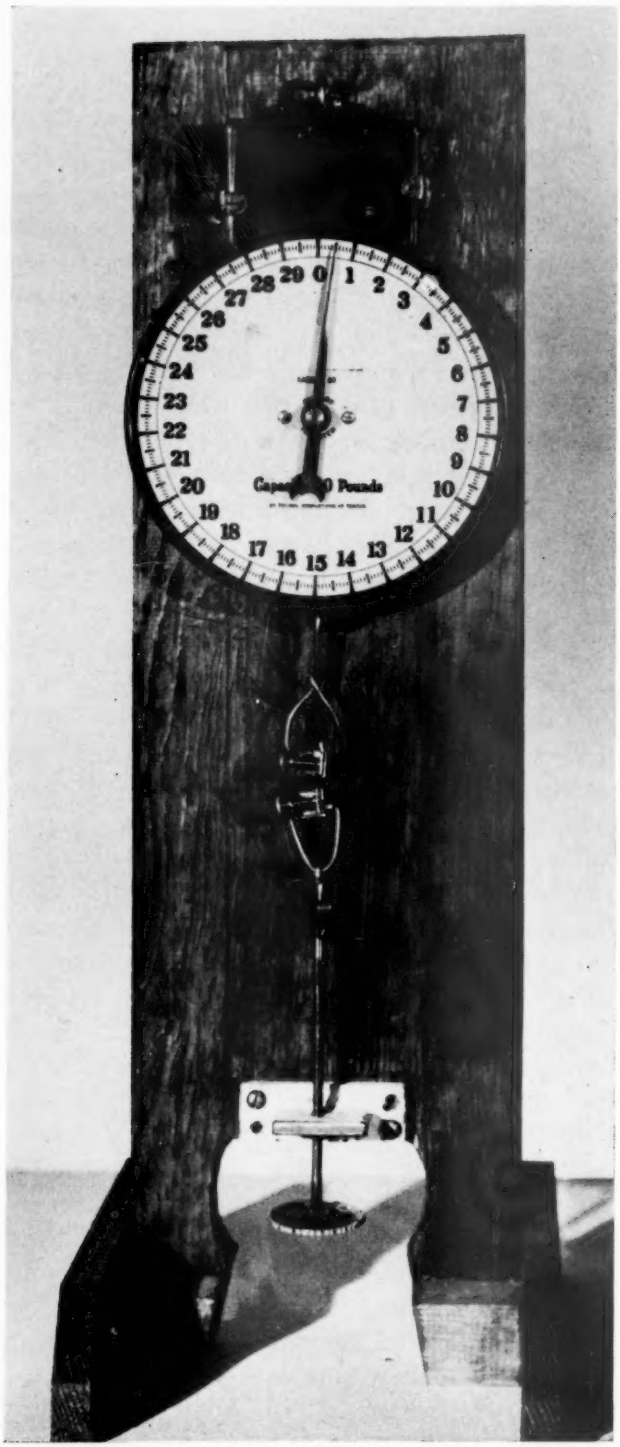


Fig. 4.—Photograph of tensiometer. Tendon is wrapped in emery paper and placed in two screw clamps. Clamps are tightened and longitudinal traction is applied through tendon by turning large screw head shown at the lower portion of the apparatus. The pull necessary to break the tendon is measured in pounds. This is subsequently converted to grams per square millimeter of tendon cross section.

as stronger than the maximum reading and no further attempts were made to measure their actual strength. In the early part of the experiment the actual strength of a few tendons was not determined and only gross determinations of strength of union were made. This was done by attempting to break the tendon union by fixing clamps to each end of the tendon and exerting traction in opposite directions. If the union withstood vigorous traction, it was deemed strong and so reported. Other tendons were saved for microscopic examination and their union was similarly tested and reported. By these methods it was possible to obtain comparative values of strength of tendon union following primary suture within the flexor tunnels.

The derivation of a method for measuring function was far more difficult than for that of measuring strength. Ideally, one would like to measure the number of degrees of active flexion and extension of the digits in the normal dog and compare it to the experimental digits. Unfortunately, it was impossible to do this in the experimental animal since this necessitated voluntary action on the part of the animal. The next best procedure was to measure the passive excursion of the tendon within the digit, plus the degree of adherence of the tendon within the tunnel, and to compare these values with those found in the normal dog. In the intact normal dog the distal portion of the profundus tendon moved 3 to 4 mm. when traction was applied to the palmar segment of the profundus tendon; after cutting the tendon distally, it was impossible to withdraw it from the tunnel by traction applied proximally. If the sublimus was excised from the tunnel and the vinculum dissected away from the palmar segment of the profundus, the distal portion of the tendon moved 3 to 8 mm. when traction was applied proximally; and after cutting the tendon distally, it could be easily withdrawn from the tunnel.

Since in this experimental method the sublimus tendon was partially removed, the profundus, in this situation, would normally have a distal excursion of 3 to 8 mm. and if the tendon were transected distally it could easily be withdrawn from the tunnel. If the experimental tendon behaved in a similar manner it was graded as normal (*3 plus function*). Lesser degrees of function were graded as follows: *2 plus function*, 1 to 3 mm. excursion of the distal tendon, and the ability to withdraw the tendon from the tunnel after distal division of the tendon with moderate to strong traction applied proximally; *1 plus function*, 1 to 3 mm. excursion of the distal tendon, yet inability to withdraw the transected tendon from the tunnel; *0 function*, no excursion of distal tendon, and inability to withdraw the transected tendon from the tunnel. In addition, an unhealed tendon was graded as having 0 function.

Thus, function of the tendon following primary suture within the tunnel has been designated by objective functional grades ranging from 0 to 3 plus, indicating the stages between nonfunction and normal function.

SUMMARY OF METHOD

(1) The anatomy of the flexor mechanism of the forefoot of the dog is essentially the same as that in the human hand, and presents a situation ideal for well-controlled experiment. (2) A quantitative method for determining the strength and a system of grading function from 0 to 3 plus following primary

tendon repair within the flexor tunnels is described. (3) Primary tendon repair employing meticulous asepsis, bloodless field, atraumatic technique, and plaster cast immobilization was accomplished by utilizing Bunnell's removable tension wire, a single (basket-weave) suture anastomosis, and experimental tubes to block the extratendon tissues. Every procedure was accompanied by a control.

EXPERIMENTAL RESULTS

1. *Search for experimental membrane suitable for use in the "block" technique.*—At first it was thought that absorbable materials would best be suited for this technique, with the hope that the material would stay present long enough to prevent cross growth of adhesions and would then slowly melt away, obviating any necessity for a secondary removal of the material as was the case with metallic tubes. With this idea in mind, gelatin was first tried. This material is a supposedly nonirritating, absorbable protein. It was possible to mold tubes from moistened sheet gelatin, harden the tubes in 10 per cent formalin, and use these tubes in the "block" technique. Unfortunately, the gelatin tubes gave a marked tissue reaction with the formation of dense adhesions and were not suitable for our purpose. The failure of the gelatin tubes was probably due to the irritating qualities of the formalin used to plasticize them.

Cellulose acetate phthalate was next tried. This material is used commercially as an enteric coating for medicaments. Preliminary tests showed this material causes no tissue reaction. By plasticizing with 70 per cent alcohol, it can be molded into tubes. Five tendons were blocked with phthalate tubes. However, the material was broken down too quickly (three days) for the tubes to function as a blocking mechanism.

Gelfoam and fibrin film tubes were similarly tried on seven tendons. These tubes also disappeared too soon to achieve the desired results. At this point, absorbable plastics were abandoned in favor of nonabsorbable materials.

At about this time, Grindley[16] reported on a new substance, polyethylene film.* His work indicated that this material was singularly nonirritating in tissues. It was commercially available as film in varying thicknesses, and as thick-walled tubes. The film proved to be particularly adaptable for my work. Because of its low melting point (110° C.) it was possible to make single layer tubes of thin (.003 inch) film by folding the film and heat-sealing the open edges. The tubes thus formed were exceptionally pliable and durable. These prefabricated tubes were used about primary repairs. In secondary repairs, after primary healing of the tendon, but where adhesions caused loss of function, a tube was constructed at the time of operation by encircling the freed tendon with a single layer of film and heat-sealing the clamped free edges. In the experimental series concerned with primary suture of the profundus tendon within the flexor tunnel, standard tubes of .003 inch polythene film measuring 2 cm. in length and 4 mm. in diameter were used. Thirty polythene tubes were

*Commercially known as polythene. The materials used in this study were supplied by the Visking Corporation of Terre Haute, Ind. Polythene is made by polymerizing molecules of ethylene under high pressure. The result is macromolecules consisting of long carbon chains in which each carbon bears two hydrogen atoms. Polythene is simply a glorified paraffin in which the chain molecules are very much longer than in ordinary household paraffin.

used about tendons. No gross or microscopic reaction to the polythene was ever noted.

Polythene film proved to be a suitable material for use in the "block" technique because of its tissue inertness, flexibility, and its adaptability to tube manufacture.

2. *Healing of tendons within polythene tubes.*—Twenty-five profundus tendons were divided, sutured in the flexor tunnels, and surrounded by polythene tubes (Table I). The suture lines were completely blocked away from the extra-tendon structures. The tendons were immobilized by tension wires and casts from eight to sixty-five days. The tubes were left in place from twelve to seventy-nine days. Not only did healing occur within the tubes but strong healing occurred when the period of immobilization was forty days or longer. A summary of the tensile strength of the tendons, measured in grams per square millimeter, can be found in Fig. 5.

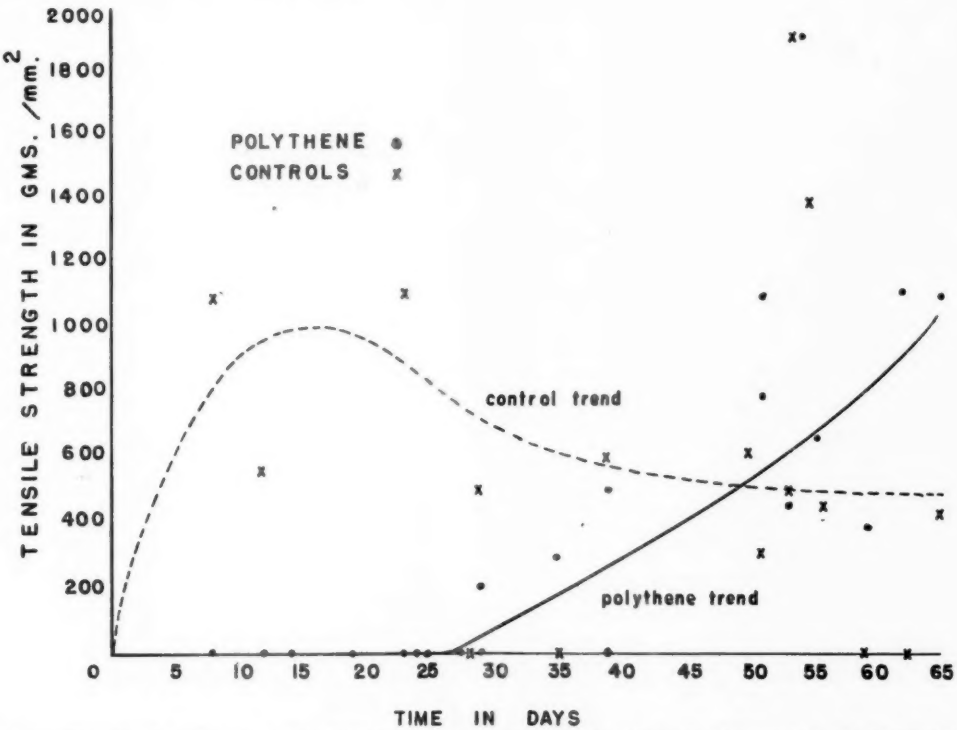


Fig. 5.—Graph showing the relationship of strength of healing to the period of immobilization in the polythene-blocked tendon repairs and in the controls.

As can be seen, the control tendons healed much earlier than the polythene tendons. No tendon protected by a polythene tube healed before twenty-nine days. After twenty-nine days, strength of union increased rapidly. The average tensile strength of polythene tendons immobilized forty days or longer was 785 Gm. per square millimeter. The average control tendon for the same period was 624 Gm. per square millimeter. These values demonstrate that if immobilization is prolonged, strong healing does occur in "blocked" tendons. That these values are an indication of actual strong healing is confirmed by

TABLE I

NUMBER OF WEEKS IMMOBILIZATION	DOG NO.	WT. (IN KG.)	PERIODS OF IMMOBILIZATION (IN DAYS)	PERIOD BETWEEN REMOVAL OF IMMOBILIZATION & EXAM	TENDON STRENGTH (IN GM. PER SQ. MM.)		TENDON FUNCTION				REMARKS
							CONTROL		POLYTHENE		
					CONTROL	POLYTHENE	FINDINGS AT EXAM	FUNCTION GRADE	FINDINGS AT EXAM	FUNCTION GRADE	
	48-246	16.0	8	71	1111	$\overline{0}$	No movement of tendon; dense adhesions	0		0	Aire-lite cast used instead of plaster; accounts for early loss of immobilization
1-2	48-301	15.25	12	0	567	$\overline{0}$	2 mm. movement of distal tendon; tendons can be withdrawn from tunnel with strong traction	2+		0	Dog died; pneumonia, accounts for early exam
	48-68	18.0	14	54	Good	$\overline{0}$	2 to 3 mm. transmitted movement of distal tendon; impossible to withdraw tendon	1+		0	
	48-79	8.25	19	6	$\overline{0}$	$\overline{0}$		0		0	
	48-216	20.0	22	7	$\overline{0}$	$\overline{0}$		0		0	
	48-233	13.5	23	18	1137	$\overline{0}$	1 to 2 mm. transmitted movement of distal tendon; tendon can be withdrawn with extreme traction	2+		0	
2-4	48-303	13.0	24	0	Strong	$\overline{0}$	No movement of tendon; impossible to withdraw tendon	0	Tendon broke on withdrawal	0	
	48-213	10.75	26	9	Very strong	$\overline{0}$	2 to 3 mm. transmitted movement of distal tendon; impossible to withdraw tendon	1+		0	
	48-81	15.25	28	19	$\overline{0}$	$\overline{0}$		0		0	Secondarily infected; pressure sores

	48-286	18.75	29	15	500	204	2 to 3 mm. transmitted movement of distal tendon; impossible to withdraw tendon	1+	5 mm. movement of tendon; tendon can be *easily* withdrawn	3+	
4-6	48-232	16.5	35	2	$\overline{0}$	270	Tendon broke on withdrawal	0	3 mm. movement of distal tendon; tendon can be *easily* withdrawn	3+	
	48-266	14.3	39	0	550	500	3 mm. transmitted movement of distal tendon, impossible to withdraw tendon	1+	3 mm. movement of distal tendon; tendon can be *easily* withdrawn	3+	
	48-203	15.0	39	2	$\overline{0}$	$\overline{0}$		0		0	Secondarily infected; cast sores
	48-106	13.75	47	0	Strong	Strong	No motion of distal tendon; impossible to withdraw tendon	0	3 mm. movement of distal tendon; tendon can be *easily* withdrawn	3+	Anastomosis, sectioned for microscopic exam
	48-293	11.5	49	0	Strong	Strong	2 to 3 mm. motion of distal tendon; impossible to withdraw tendon	1+	3 to 4 mm. movement of distal tendon; tendon *easily* withdrawn	3+	Anastomosis, sectioned for microscopic exam
	48-308	13.25	51	0	610	1100	3 to 4 mm. movement of distal tendon; impossible to withdraw tendon	1+	3 mm. movement of distal tendon; tendon *easily* withdrawn	3+	
6-8	48-110	24.0	51	0	330	774	3 to 4 mm. movement of distal tendon; impossible to withdraw tendon	1+	5 mm. motion of distal tendon; tendon withdrawn with moderate traction	2+	
	48-233	13.5	53	0	>1880	>1880	No motion of distal tendon; impossible to withdraw tendon	0	2 to 3 mm. motion of distal tendon; tendon *easily* withdrawn	3+	

(Continued on following page.)

TABLE I—CONT'D

NUMBER OF WEEKS IMMOBILIZATION	DOG NO.	WT. (IN KG.)	PERIODS OF IMMOBILIZATION (IN DAYS)	PERIOD BETWEEN REMOVAL OF IMMOBILIZATION & EXAM	TENDON STRENGTH (IN GM. PER SQ. MM.)		TENDON FUNCTION				REMARKS
							CONTROL		POLYTHENE		
					CONTROL	POLYTHENE	FINDINGS AT EXAM	FUNCTION GRADE	FINDINGS AT EXAM	FUNCTION GRADE	
	48-284	16.75	53	0	488	444	4 to 5 mm. transmitted movement of distal tendon; impossible to withdraw tendon	1+	4 to 5 mm. movement of distal tendon; tendon *easily* withdrawn	3+	
	48-215	18.75	54	0	Strong	510	3 mm. transmitted movement of distal tendon; impossible to withdraw tendon	1+	4 to 5 mm. movement of distal tendon; tendon withdrawn with moderate traction	2+	
	48-299	20.75	55	0	1440	645	No motion of distal tendon; impossible to withdraw tendon	0	3 mm. motion of distal tendon; tendon withdrawn with moderate traction	2+	
	48-271	15.50	56	0	446	0	1 mm. motion of distal tendon; impossible to withdraw tendon	1+	Tendon broke on withdrawal	0	
	48-215	18.75	59	0	0	370	Tendon broke on withdrawal	0	2 to 3 mm. motion distally; tendon withdraws with moderate traction	2+	
8-10	48-285	11.5	62	0	0	1111	Tendon broke on withdrawal	0	3 mm. movement of distal tendon withdraws with moderate traction	2+	
	48-203	15.0	65	0	430	1100	No movement of distal tendon; impossible to withdraw tendon	0	3 mm. movement of distal tendon *easily* withdrawn	3+	

comparison with the data presented by Mason and Allen[17] in their work on tensile strength of tendons following primary repair. The strongest union which they obtained was in tendons that were immobilized for three weeks and then allowed unrestricted activity for twenty days. The average tensile strength of these tendons was 751 Gm. per square millimeter. My figure of 785 Gm. per square millimeter for blocked tendons immobilized for forty days compares favorably with their best results.

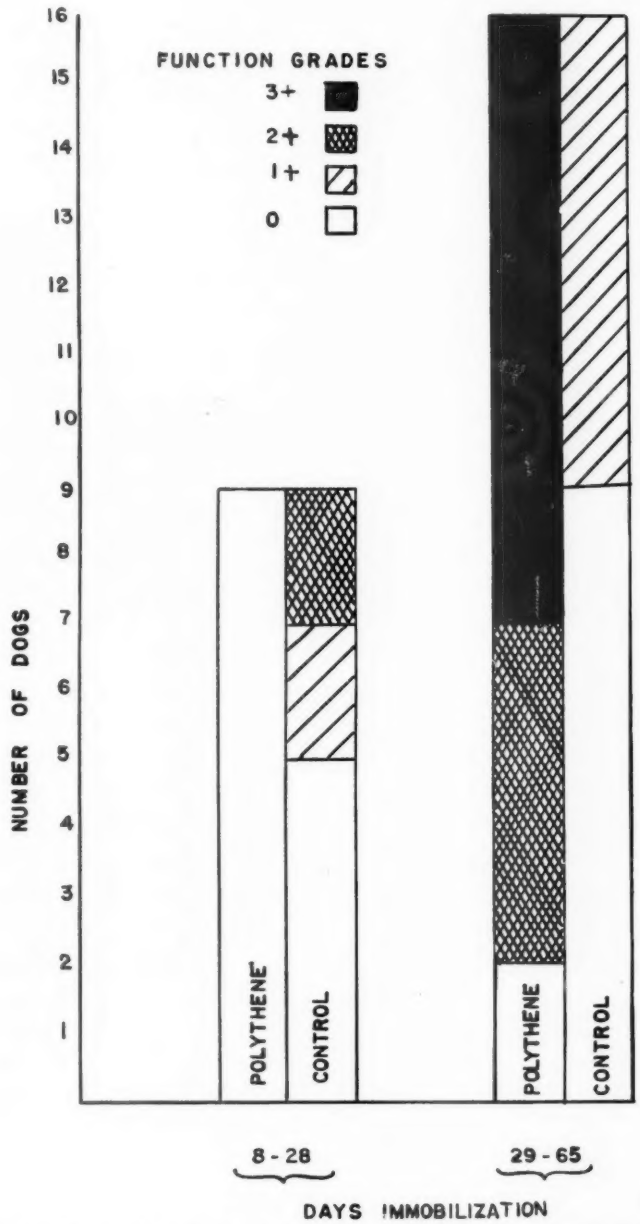


Fig. 6.—Bar diagram illustrating the functional results of tendon anastomoses blocked with polythene tubes as contrasted with the controls in terms of the period of immobilization.

In summary, flexor tendons in the dog do heal if blocked away from their extratendon tissues, but healing is delayed. If immobilization is maintained forty days or longer, however, strong union results.

3. *Functional results with use of "block" technique.*—The functional result of twenty-five experimental tendons and twenty-five control tendons were carefully graded according to the system described under Method. These functional results are summarized in graphic form in Fig. 6. The first two columns illustrate the functional results following twenty-nine days or less immobilization. No polythene tendons healed during this time interval and, therefore, they all fall into the 0 functional classification. The next two columns, however, illustrate the functional results following more than twenty-nine days' immobilization. Here, fourteen out of sixteen polythene tendons achieved a functional rating of 2 or 3 plus, while at the same time, not a single control tendon was rated better than 1 plus.

This data strongly suggests that function is greatly improved following primary suture in the flexor tunnels if the suture line is blocked away from the extratendon tissues by means of a polythene tube.

COMMENT

There are a few points other than those already discussed which were brought out during this work. One is the relation of immobilization to adhesion formation and resorption. From this work it is not possible to tell exactly when adhesions form, probably after twelve days, but some very interesting points can be emphasized about their resorption and differentiation. Mason and Allen[17] noted striking changes in the amount and the extent of adhesion formation in tendons immobilized for long periods of time. They stated, "The gross appearance of tendons immobilized 4-5 weeks has direct practical significance. They were seen to be beautifully healed; the tissues about them were transparent and areolar and glided over the surface of the tendon, and tendon itself glided through them." In the experiments reported here, a similar differentiation of the extratendon tissues was noted in the control tendons that were immobilized for thirty-five days or longer. The operative area in tendons immobilized for shorter periods of time was a solid mass of scar tissue. It was impossible to differentiate the tendon from the sheath or tunnel. However, following long periods of immobilization (thirty-five days or more) there was a clear differentiation of the structures. The adhesions were filmy and translucent. It was easy to dissect the tendons away from the extratendon tissues. In the control tendons, since the work was being done in the tunnels, unlike Mason and Allen, it was impossible to demonstrate free gliding of the tendons. Nevertheless, this differentiation of tendon, adhesions, and extratendon tissues would argue for longer periods of immobilization than now advocated, no matter what type of primary repair is employed.

The other point, really a suggestion, is the possible use of polythene film about tendons that have healed primarily but are bound down by adhesions. After the adhesions have been dissected away from the tendon, polythene film could be wrapped about the tendon and thus prevent the infiltration of adhesions.

TABLE II. SECONDARY WRAPPING OF HEALED TENDONS WITH POLYTHENE FILM

DOG NUMBER	WT. IN KG.	DAYS IMMOBILIZATION FOLLOWING PRIMARY SUTURE	DAYS IMMOBILIZATION FOLLOWING SECONDARY WRAP	TENDON STRENGTH (IN GM. PER SQ. MM.)		TENDON FUNCTION			
						CONTROL		POLYTHENE	
				CONTROL	POLYTHENE	FINDINGS AT FINAL EXAM	FUNCTION GRADE	FINDINGS AT FINAL EXAM	FUNCTION GRADE
48-246	16.0	10	7	880	>1,000	No movement of distal tendon; impossible to withdraw tendon	0	2 to 3 mm. movement of distal tendon; impossible to withdraw tendon	1+
48-216	20.0	15	24	$\overline{0}$	$\overline{0}$	No primary healing	0	Broke on withdrawal	0
48-240	23.0	32	18	66	$\overline{0}$	No movement of distal tendon	0	Broke on withdrawal	0
48-267	14.75	37	7	>308	> 340	2 to 3 mm. movement of distal tendon; tendon withdrawn with strong traction	2+	3 mm. movement of distal tendon; tendon withdrawn with mild traction	3+
48-244	16.0	44	40	700	3,250	No movement of distal tendon; impossible to withdraw tendon	0	3 mm. movement of distal tendon withdrawn with mild traction	3+

A short experiment of a series of five animals was carried out with this idea in mind. These results are tabulated in Table II. It can be seen that excellent results followed secondary wrappings done on tendons whose primary repair had been immobilized for thirty-five days or longer, long enough for differentiation of the structures to occur. In these tendons it was easy to free the adhesions. In tendons immobilized less than thirty-five days, the dissection was far more difficult because of lack of differentiation between tendon and adhesion. The secondary wrapping of tendons is believed to be a promising procedure and should be investigated further. If the period of immobilization following primary suture is thirty-five days or longer, tendolysis followed by polythene wrapping might prove to be extremely valuable in restoration of tendon function.

SUMMARY AND CONCLUSIONS

1. An experimental method for the investigation of primary tendon repair within the flexor tunnels in the dog is presented.

2. The use of absorbable and nonabsorbable tubes to block the cross growth of adhesions from tendon to extratendon tissues has been investigated.

3. Tubes made of thin polythene film were found to be most suitable for this purpose because they are flexible and cause no tissue reaction.

4. Tendons heal strongly within polythene tubes if immobilized forty days or longer.

5. Tendons blocked away from the extratendon tissues by polythene tubes following primary suture within the flexor tunnels and immobilized forty days or longer approach normal function while control tendons approach nonfunction.

REFERENCES

1. Bunnell, Sterling: Personal Communication.
2. Bunnell, Sterling: Surgery of the Hand, Philadelphia, 1944, J. B. Lippincott Company.
3. Cootes, J. Chaphan: Correspondence, Cut Tendons, Brit. M. J. **1**: 212, 1941.
4. Teece, L.: Treatment of Wounds of the Hand, M. J. Australia **2**: 332, 1939.
5. Mouat, T. B.: Section on Tendons; Bailey H. (editor), Surgery of Modern Warfare, Edinburgh, 1941, E. & S. Livingstone, p. 364.
6. Miller, H.: Repair of Severed Tendons of the Hand and Wrist, Surg., Gynec. & Obst. **75**: 693-698, 1942.
7. Posch, J. L.: Primary Tendon Repair, S. Clin. North America **28**: 1323-1340, 1948.
8. Koch, S. L.: Division of the Flexor Tendons Within the Digital Sheath, Surg., Gynec. & Obst. **78**: 9-22, 1944.
9. Mason, M. L.: The Treatment of Open Wounds of the Hand, S. Clin North America 28: 4-26, 1948.
10. Mayer, L., and Ransohoff, N.: Reconstruction of the Digital Tendon Sheath, J. Bone & Joint Surg. **18**: 607-616, 1936.
11. Wilmoth, C. L.: Tendinoplasty of the Flexor Tendons of the Hand, J. Bone & Joint Surg. **19**: 152-156, 1937.
12. Davis, L., and Aries, L. J.: An Experimental Study Upon the Prevention of Adhesions About Repaired Nerves and Tendons, SURGERY **2**: 877-888, 1937.
13. Wheeldon, T.: The Use of Cellophane as a Permanent Tendon Sheath, J. Bone & Joint Surg. **21**: 393-396, 1939.
14. McKee, G. K.: Metal Anastomosis Tubes in Tendon Suture, Lancet **1**: 659-660, 1945.
15. Swan, H., Gonzales, R. I., Harris, A., Coulson, C., and Hopwood, M.D.: Use of a Quaternary Ammonium Compound for the Surgical Scrub, Am. J. Surg. **77**: 24-37, 1949.
16. Brown, M. H., Grindley, J. H., and Craig, W. McK.: Preliminary Report on Experimental and Clinical Studies With Polythene Film, Proc. Staff Meet., Mayo Clin. 22: 453-456, 1947.
17. Mason, M. L., and Allen, H. S.: The Rate of Healing of Tendons, Ann. Surg. **113**: 424-459, 1941.

HEMIPELVECTOMY

MARK M. RAVITCH, M.D., BALTIMORE, MD.

(From the Department of Surgery, The Johns Hopkins Hospital and University)

THE hindquarter amputation is frequently considered so mutilating a procedure and of such forbidding magnitude as to be properly excluded from the category of acceptable surgical operations. While it cannot be denied that the resultant deformity is extremely grave, it must be remembered that it is inflicted as the result of a procedure offering the only hope of cure in many otherwise ineradicable neoplasms of the upper thigh and pelvic girdle. Moreover, in the present state of operative technique and fluid replacement therapy it is a procedure well within the capabilities of any competent surgeon. Relatively few such operations are recorded despite a number of publications showing the progressive decrease in mortality. Gordon-Taylor[1] has performed 21 hindquarter amputations with 6 deaths. The last 3 patients, all of whom recovered, were operated upon subsequent to his "Presidential Address on Amputation."[1] This is still the largest single reported series of such procedures. As recently as 1942, Morton's[4] report of 4 cases with no operative mortality was outstanding. The older reports of a mortality of 75 per cent and 50 per cent have been replaced by more recent reports of as many as 8 successive operations without mortality.[6] The reports of Leighton[2] in 1942, of Sugarbaker[7] in 1945, and of Pack[5, 6] in 1946 and 1947 are among the most helpful to the surgeon planning to perform a hemipelvectomy. The present report is aimed at a clear presentation of the technical features of the operation. We wish to emphasize the essential straightforwardness of this surgical procedure rather than to present any new method for its performance. Two of the patients are of unusual interest, one in whom amputation was performed for a Marjolin's ulcer, and another, a 12-day-old infant, with extensive and deforming lymphangiomas and hemangiomas of the limb and pelvic girdle.

The term hemipelvectomy is simpler and more readily understood than the more complicated terms applied to this procedure. Malignant tumors of the upper thigh which invade the pelvis or the muscles attached to the pelvis are probably more safely removed by hemipelvectomy than by hip joint disarticulation. A moment's reflection will show that, from the standpoint of numbers of structures and muscle masses to be divided, the hemipelvectomy is a simpler procedure than the hip joint disarticulation. Anteriorly in the hemipelvectomy the only muscle divided is the psoas. Posteriorly the quadratus, piriformis, and the gluteus maximus at its origin are the only muscles to be divided, aside from the levator ani and ischiocavernosus. The final wound is certainly easier to close than the wound left by a hip joint disarticulation. From the standpoint of functional disability, there is little to choose between the two operations, since a prosthesis is not likely to be worn after either procedure. A few descriptions of such prostheses may be found.[3]

Received for publication, Oct. 22, 1948.

Hemipelvectomy has been performed for every variety of malignant tumor. It seems probable that the greatest success will be achieved with such slow growing lesions as chondrosarcoma and lipomyxoma, which form extensive local tumors but metastasize late, so that a sufficiently radical procedure may effect a cure. The squamous-cell carcinoma (Marjolin's ulcer) of the first patient is an unusual lesion to require this operation.

TECHNIQUE

The type of anesthetic agent is immaterial, both general and spinal anesthesia having been used. The choice here has been pentothal anesthesia with nitrous oxide supplement. The bladder is emptied and the catheter left as a guide to the urethra. The lower abdomen is included in the field. Medially the towels are clipped to the side of the genitals in front, and alongside the anus behind. With the extremity draped free, the opposite side of the sacrum and the shoulder of the same side are elevated on sandbags to permit easier manipulation of the limb. The hip and thigh on the operative side are thus lifted off the table, facilitating the posterior phase of the procedure.

Anteriorly the incision extends from the symphysis to the anterosuperior spine and then for several inches along the iliac crest. The lateral insertion of the inguinal ligament is detached from the anterosuperior spine and its medial portion is separated from the pubis together with the rectus and pyramidalis insertions after the fascial attachments to the iliopectineal fascia are divided. The deep epigastric vessels thus exposed are ligated and divided. Blunt dissection then strips away the peritoneum and exposes the iliac fossa widely (Fig. 1). One can easily see the external and internal iliac vessels, the ureter and bladder, and the rectum behind the peritoneum. The external iliac vessels have been ligated in this series, since some reports have remarked upon necrosis of the central portion of the posterior flap, if the common iliac vessels are divided. Pack[5] advocated ligation of the common iliac artery for greater comfort in the posterior dissection and suggested prophylaxis of the slough in the posterior flap by a V-shaped excision of the central portion. The psoas muscle is divided at a convenient level. There is no notable bleeding. The femoral nerve thus exposed is ligated and divided. This completes the anterior dissection except for the symphysis pubis. By dissection with fingers and periosteal elevator, the symphysis is exposed. A curved clamp is forced through the space between the urogenital diaphragm and the symphysis to grasp a Gigli saw by which the symphysis is divided. In either sex the large plexus of veins behind the pubis may cause troublesome bleeding which is controlled temporarily by packing. The division of the psoas muscle with the femoral nerve, the external iliac vessels, and the symphysis constitutes the anterior phase of the operation.

The incision is now continued posteriorly. The tendency is to fashion too generous a flap posteriorly and, while time will be saved by fashioning a short posterior flap, the danger of closure under tension must be kept in mind. From the posterosuperior iliac spine the incision sweeps down around the buttock, well above the trochanter, and passes around to meet the an-

terior incision two or three inches from the midline. The short posterior skin flap is elevated and the origins of the gluteus maximus divided. There appears to be no virtue in preserving the gluteus maximus. This muscle is lifted forward, the patient's hip is flexed and adducted, and the piriformis muscle is exposed with the superior and inferior gluteal vessels at its upper and

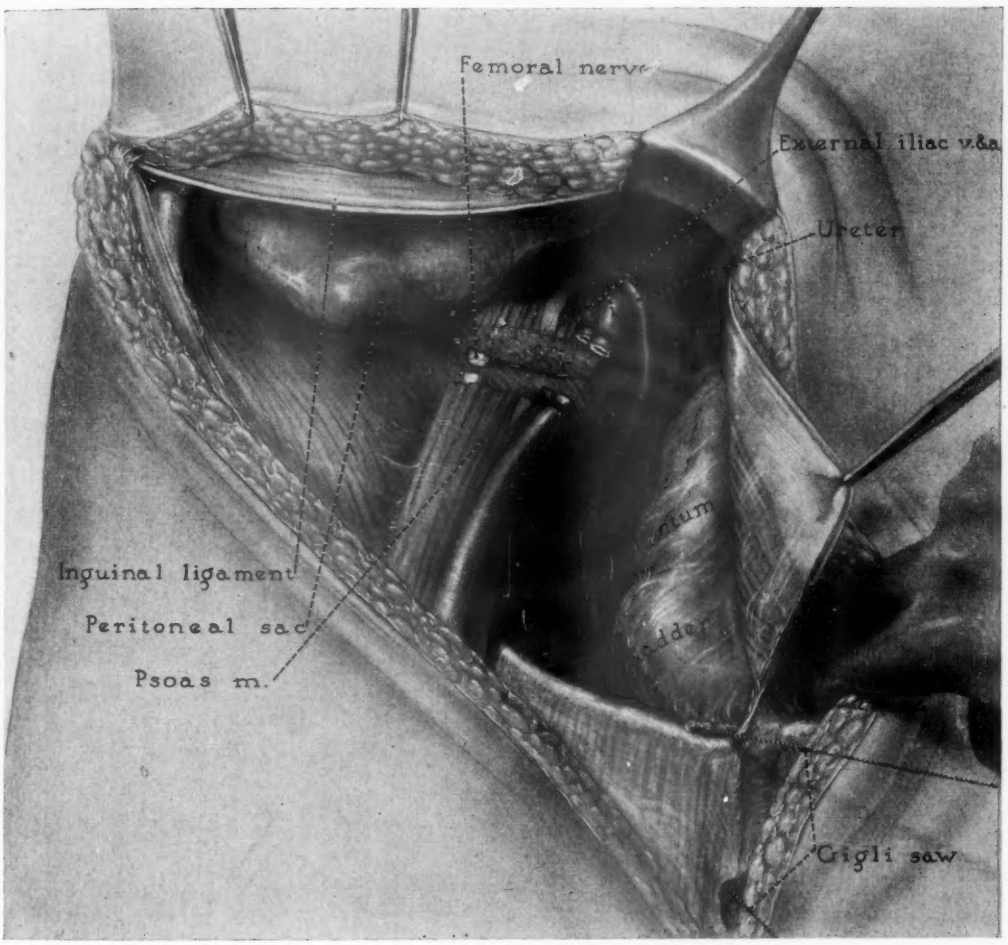


Fig. 1.—The inguinal ligament has been detached at both ends and the rectus and pyramidalis muscles have been separated from the pubis. The peritoneum has been stripped back revealing the contents of the iliac fossa. The external iliac vessels, psoas muscle, and femoral nerve have been divided. A Gigli saw has been pased around the symphysis. The subject is a woman. In the male the spermatic cord is displaced medially.

lower borders, respectively (Fig. 2). These vessels are secured and the piriformis muscle is transected, exposing the sciatic nerve which is ligated and divided. The tough sacrospinous and sacrotuberous ligaments are divided. One need only divide the quadratus lumborum muscle close to the ilium to complete the posterior dissection. A Gigli saw can now be passed around the sacroiliac joint which is cut through (Fig. 3). If the tumor has not invaded the bony pelvis, there is no harm in leaving a fragment of ilium attached to the sacrum. It will now be found that the hindquarter is attached only by

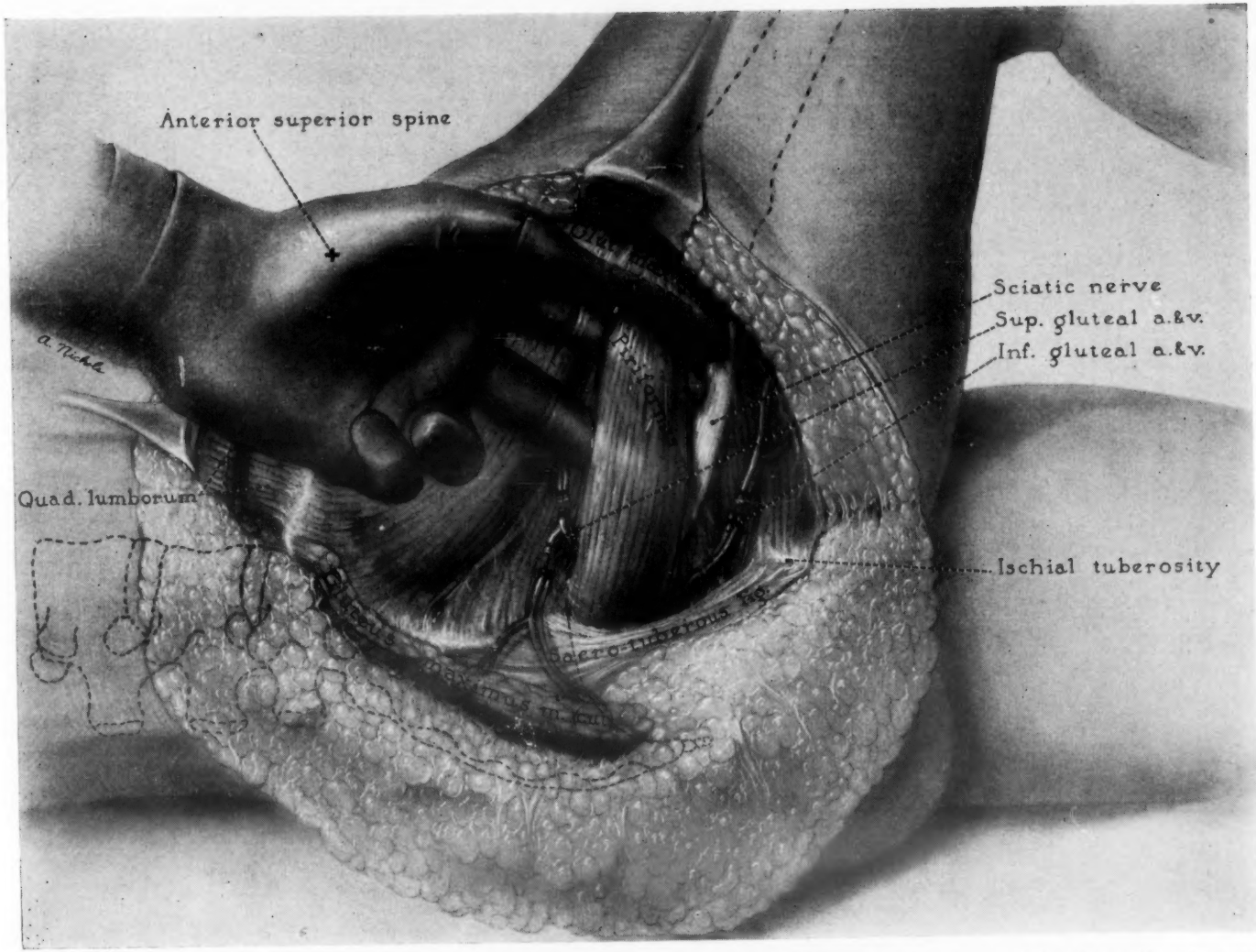


Fig. 2.—The hip is flexed and adducted and the patient leaned to the opposite side. The incision is continued posteriorly from the posterior superior iliac spine to pass around the thigh well above the greater trochanter. The gluteus maximus is divided near its origin, the gluteal vessels are secured, and the piriformis muscle is divided. The quadratus lumborum has already been transected. The sacrotuberous and sacrospinous ligaments and the sciatic nerve will be divided next.

the levator ani and ischiocavernosus muscles. The levator ani muscle is cut through and the ischiocavernosus muscle is clamped, divided, and transfixed. With the specimen removed, bleeding from the retropubic veins can be readily controlled by mattress sutures over strips of gelatin sponge. The relative simplicity of the procedure, despite its magnitude, is apparent. The bony pelvic ring has been divided in two places. Three muscles of significance—

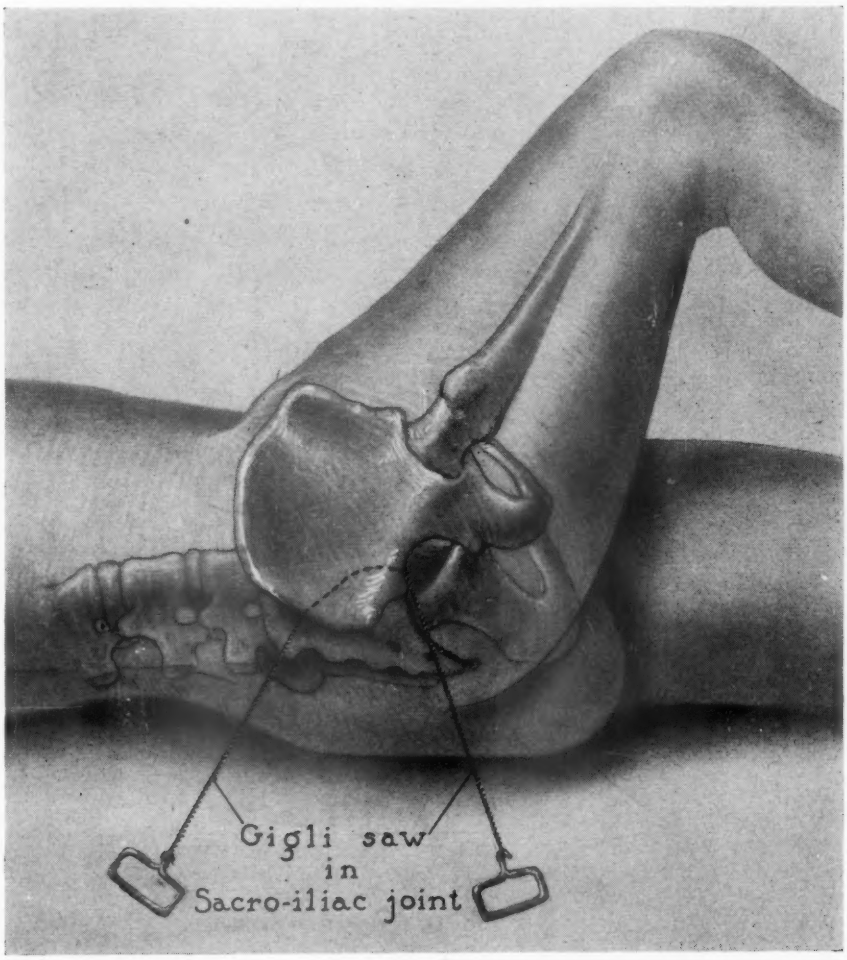


Fig. 3.—All the soft tissues posteriorly have been divided and a Gigli saw is passed through the pelvis around the sacroiliac joint, which is cut through. When this has been done, the limb will remain attached only by the ischiocavernosus and a few fibers of the levator ani.

the psoas, quadratus lumborum, and piriformis—have been divided through their bellies. The gluteus maximus has been divided at its origin. The iliac and gluteal vessels, and the femoral and sciatic nerves complete the short list of important structures divided. The levator ani and ischiocavernosus muscles are taken almost in passing, and disengagement of the attachments of the inguinal ligament anteriorly and of the sacrospinous and sacrotuberous ligaments posteriorly are simple and bloodless maneuvers.

In the anterior dissection it is important to open the iliac fossa widely, while in the posterior portion one must carefully reflect the gluteus maximus muscle to expose the gluteal vessels which are then readily ligated.

COMPLICATIONS

The urethra was injured in one patient (Case 1), in whom the nature of the primary disease required sacrifice of the right half of the scrotum and its contents. Primary repair was unsuccessful and healing was delayed. In one patient the vagina was incised. The wound was repaired and healed per primam.

Hernias have not been reported after this operation and skin closure is all that is required. Because the peritoneum and its contained bowel tend to fall over the sharp edge of the transected sacrum, we have tacked the lateral edge of Poupart's ligament to the anterior edge of the cut surface of the sacrum, protecting the peritoneum and the bowel from possible injury. A drain is laid in place at either end of the incision, the subcutaneous tissues are approximated with silk, and the skin is closed with silk sutures.

Shock has not been a problem. Transfusions were given to all patients from the start of the operation. Distention did not occur. The second and third patients were out of bed on crutches the day after operation and left the hospital on the twenty-first and sixteenth day, respectively, their wounds having healed per primam. The first patient had a preliminary colostomy with consequent prolongation of his convalescence. The two men patients had temporary loss of sexual powers. Anemia has not been observed as a postoperative phenomenon.

CASE REPORTS

CASE 1 (173005).—H. M. was a white man, aged 40 years. This remarkable man had a congenital or neonatal paraplegia with an extreme flexion deformity. He had spent most of his life sitting on the shrunken, deformed lower extremities. At the age of 10 years he developed an ulcer of the right buttock which was excised as a "trophic sore." In retrospect, it seems more likely to have been an ulcerated bursa due to pressure by the right heel on the buttock as a result of the deformity which doubled the legs beneath him. Despite repeated operations the wound never healed, and in the next thirty years he developed many communicating sinuses of the thigh, hip, and right scrotum. General health was good and he had become an accomplished silversmith and engraver. Finally, on June 23, 1946, operation was undertaken* for radical excision of all the sinus tracts. It was discovered that the right buttock was invaded by a solid tumor, growing into the pelvis, so that the attempt at complete excision was abandoned. Fig. 4 shows the condition after this operation. Pathologic study revealed the tumor to be a squamous-cell carcinoma. This was then a Marjolin's ulcer developing in thirty-year-old sinus tracts which had presumably resulted from incision of an adventitious bursa.

Hemipelvectomy seemed the only feasible operative approach, complicated by the large area of skin involved, closely approaching the anus, and invading half of the scrotum. Rectal examination showed no pelvic mass. There had been lifelong urinary frequency and difficulty in control. In view of the proximity of the sinus tracts to the anus and of the possibility that the rectum might have to be sacrificed, a sigmoid colostomy was performed on Feb. 8, 1946, after exploration of the pelvis and abdomen showed no metastases.

*By Dr. William E. Grose.

Eight days later hemipelvectomy was performed. It was rendered difficult by the patient's severe skeletal deformities. Thus, the anterior surface of the lumbar vertebral bodies pressed against the right iliac crest. The operation required 3½ hours, during which time the patient received five pints of blood and 250 c.c. of plasma without any change in general condition. Because all the skin of the buttock and the right scrotum with its contents had to be removed, an anterior skin flap was fashioned. The posterior incision actually crossed the midline, skirting the anus.

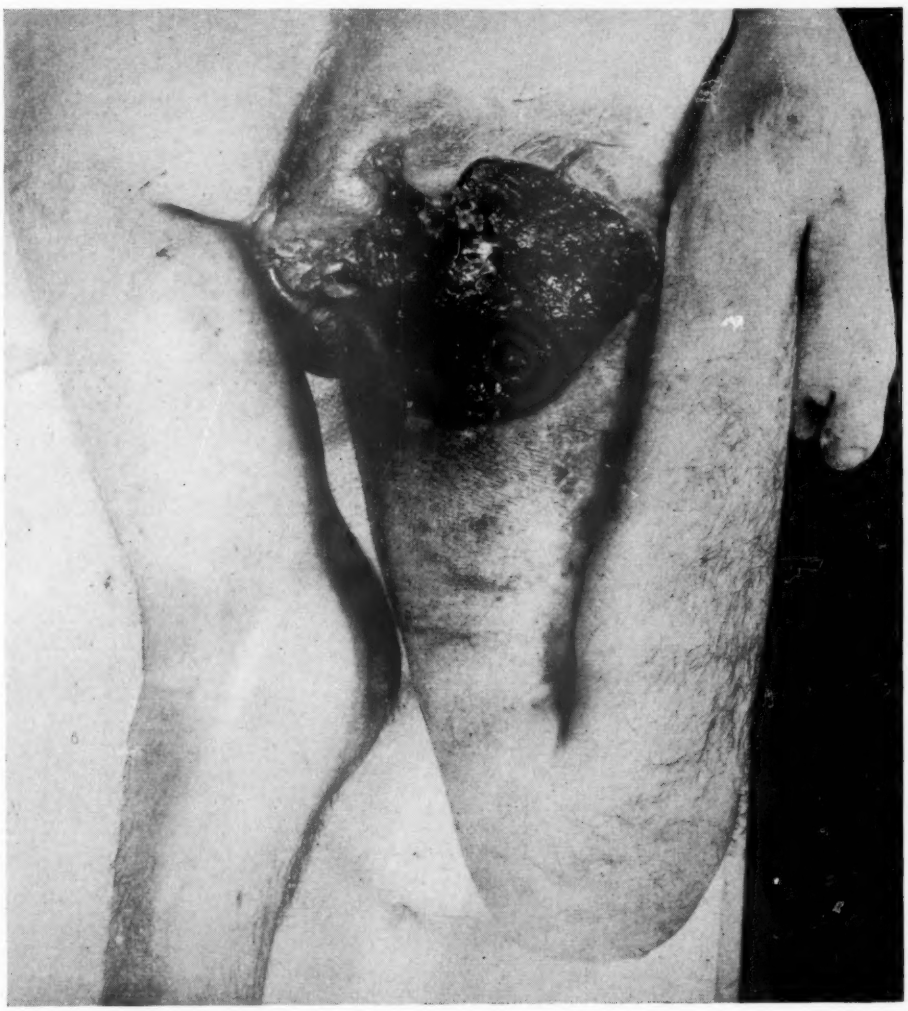


Fig. 4 (Case 1).—H. M. (J.H.H. 173005). Squamous carcinoma (Marjolin's ulcer) in numerous sinus tracts penetrating deeply through right buttock. A recent attempt at direct excision was balked by the extent of the tumor into the pelvis. The right heel, held out of the way for this photograph, ordinarily rested against the area of the ulcer.

Pathologic Report.—On the buttock and upper thigh was a large excavated ulcer 20 cm. in diameter. The surrounding skin was rolled and hypertrophied and sinus tracts led from the ulcer through the fascia and muscle. The base of the ulcer was thick, indurated, and heavily scarred. The ulcer base extended toward the symphysis and down to the obturator foramen, both sides of which were covered by dense indurated scar. Microscopic examination of the ulcer showed a well-differentiated squamous-cell carcinoma. There were no metastases in the lymph nodes.

Fig. 5 (Case 1).—Jan. 7, 1947, eleven months after amputation. The right scrotum and its contents were removed at the original amputation. Note the use made of the remainder of the scrotum in closing the wound. The dressing on the left covers the incision left after closure of the colostomy a few days before this photograph was made.

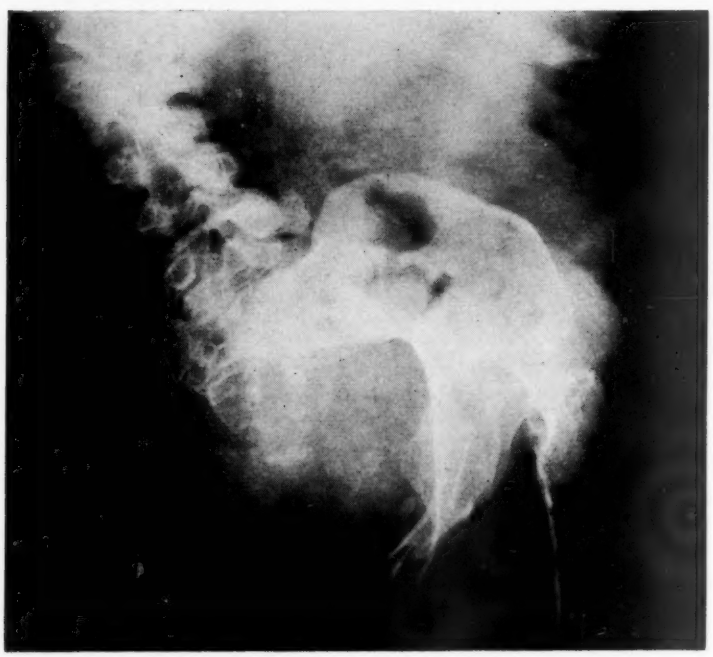


Fig. 6 (Case 1).—Postoperative roentgenogram. The atrophied femur and hemipelvis and the distorted spine are due to the congenital deformity.

The postoperative course was marked by a slowly developing hematoma and a separation of a portion of the wound. A small urethral fistula developed through the wound, entailing long use of a retention catheter. This was complicated in turn by the development of a vesical calculus which required a suprapubic cystostomy. However, he made a complete recovery from this series of difficulties and finally the colostomy was closed (Fig. 5). Sphincter control was normal. He gained over thirty pounds in weight and returned to full employment. It took a considerable period of time before he felt comfortable in sitting. Sexual power was temporarily lost but eventually returned. Two and one-half years after operation he shows no metastases and is in good health.

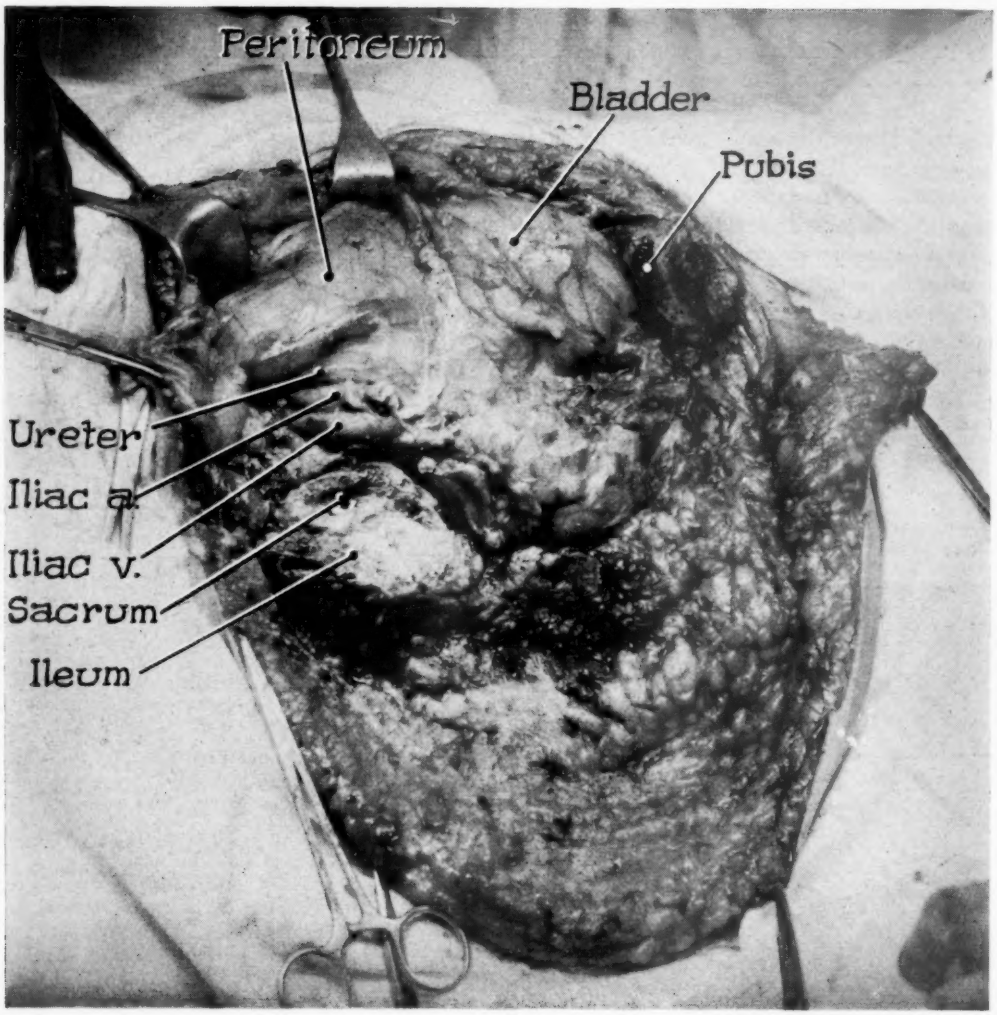
Summary.—A 40-year-old man with a congenital paraplegia developed a Marjolin's ulcer with carcinomatous invasion of the buttock and pelvis. Hemipelvectomy was performed after preliminary colostomy. Partial wound separation, a urethral fistula, and a vesical calculus complicated recovery. He is well two and one-half years after operation.

A. *B.*

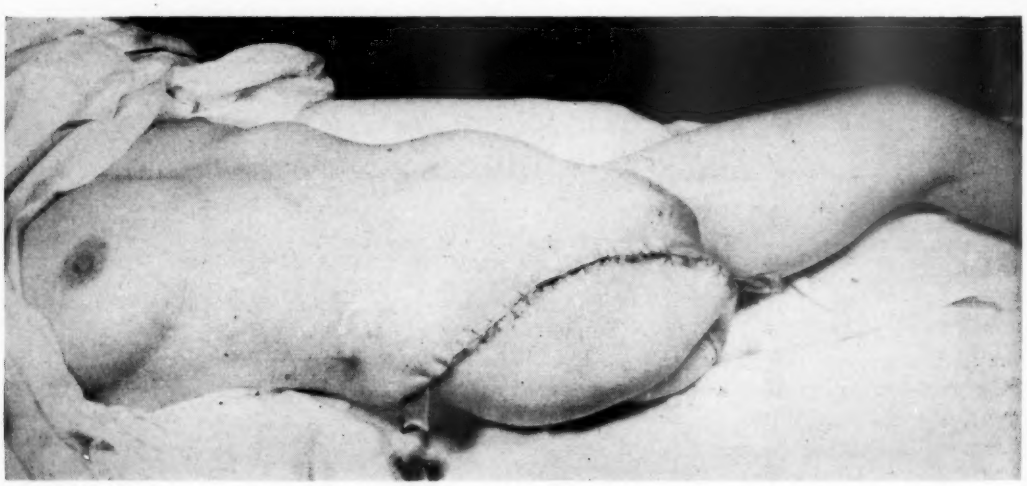
Fig. 7 (Case 2).—J. T. (J.H.H. 448545). Osteogenic sarcoma of upper femur. *A*, There is a biopsy incision. Note the swelling reaches the groin. *B*, Roentgenograms show extensive bone formation and the high level of the tumor.

CASE 2 (448545).—J. T. was a 50-year-old white woman. Eight months before admission the patient noticed discomfort in the right thigh. After one month, severe nocturnal aching pain made its appearance and she noted swelling of the thigh. The swelling increased progressively and finally two weeks before admission she gave up working. In the last two or three weeks she had become alarmed and worried and had lost about ten pounds in weight. There were no other symptoms.

Physical examination was negative except for the right thigh. The upper third was involved in a large, firm, poorly outlined swelling beginning just below the inguinal ligament



A.



B.

Fig. 8 (Case 2).—*A*, Wound just before closure is begun. The saw has cut through the sacroiliac joint at an angle, leaving a fragment of ilium posterior to it. The stumps of the iliac vessels are plainly seen. The lateral portion of the inguinal ligament will be sutured to the anterior edge of the sacrum in order to protect the peritoneal sac from the sharp edge. *B*, Appearance of wound at time of closure.

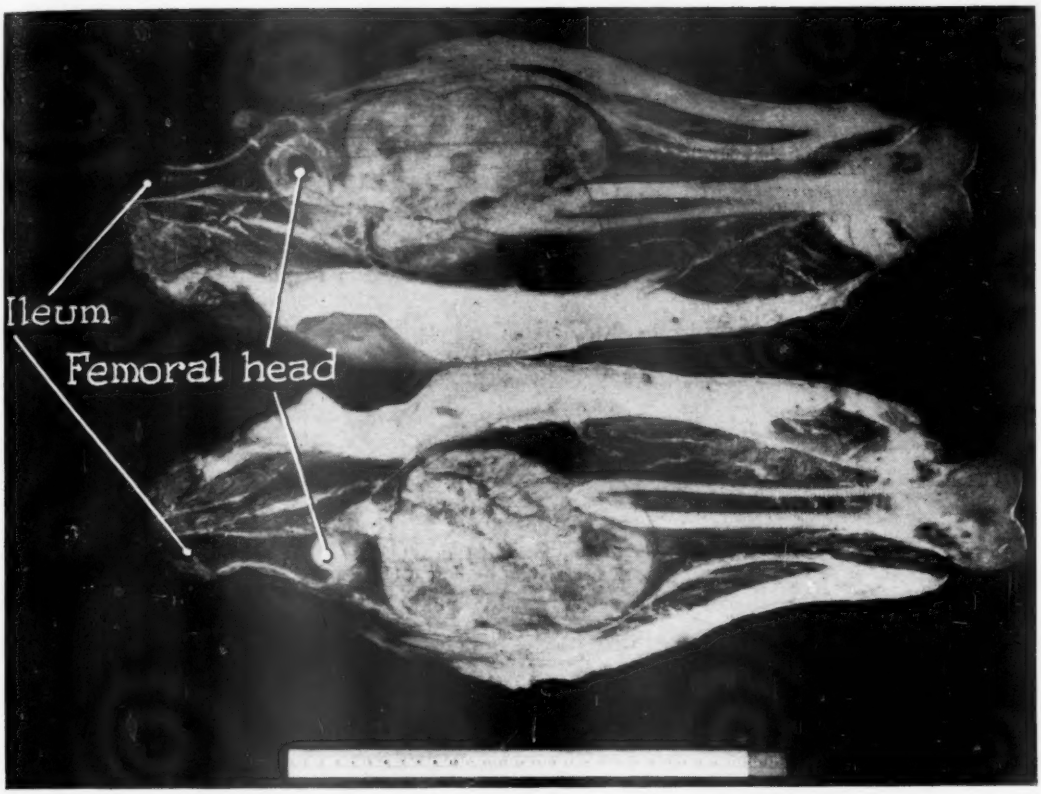
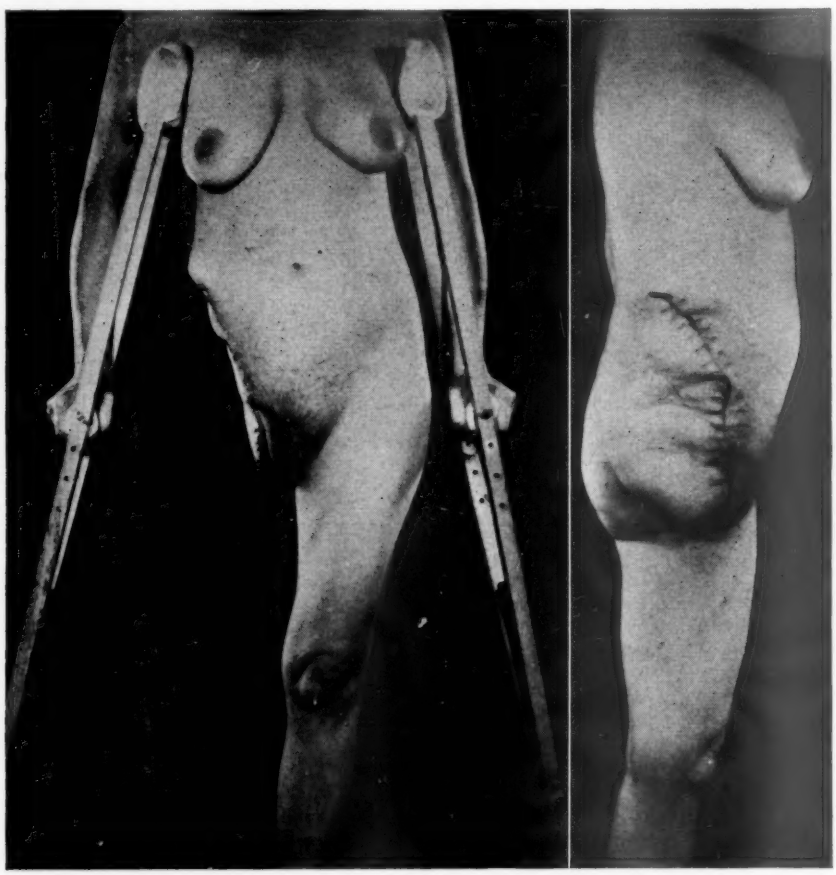


Fig. 9 (Case 2).—Specimen bisected. Note what scant margin would have been afforded by a hip joint disarticulation.

Fig. 10 (Case 2).—Postoperative roentgenogram. In this instance a fragment of ilium and a fragment of pubis remain. Had the tumor involved the bony pelvis, these bones would have been completely resected.

and fixed to the deep tissues (Fig. 7, *A*). Roentgenograms (Fig. 7, *B*) showed almost complete destruction of the upper third of the femur by a large tumor mass in which there were many areas of calcification or bone formation well out in the soft tissues. Biopsy of the tumor showed a sarcoma which varied from area to area, in some places appearing like a fibrosarcoma, in others forming bone and tumor cartilage of a kind not appearing extremely malignant, although this was obviously not a pure chondrosarcoma. There were no demonstrable pulmonary or bony metastases. It appeared improbable that a hip-joint disarticulation would remove the tumor with any margin of safety, and hemipelvectomy was decided upon.



A. *B.*

Fig. 11, *A* and *B* (Case 2).—Photographs taken fourteen days after operation.

On Jan. 24, 1948, a right hemipelvectomy was performed in the manner described (Fig. 8, *A* and *B*). There was no intrapelvic extension of the tumor. The sacroiliac joint was cut through irregularly, as seen in the roentgenograms (Fig. 10), and the pubis was cut through just to the right of the symphysis. The right side of the vagina was opened and repaired with fine catgut and silk in several layers. The operation required three hours during which time the patient received a continuous transfusion of five pints of citrated blood. Her condition was good throughout. The short posterior flap was adequate for closure and a Penrose drain was left in either end of the wound. A retention catheter was left in the bladder. Hemoglobin after operation was 13 Gm. and five days later 12.5 Gm.

Pathologic Report.—There was a large, well-encapsulated tumor 14½ cm. in diameter in the upper third of the thigh, arising from the femur (Fig. 9). It was made up of a gelatinous, rather firm, grayish white material containing some cystlike areas. The microscopic

sections showed a sarcoma with numerous areas of bone formation from spindle cells of varying size and shape. There appeared to be a good deal of tumor cartilage as well as bone. The impression was osteogenic sarcoma.

On Jan. 26, 1948, forty-eight hours after operation, the patient was out of bed and learning to use crutches for the first time. The catheter was removed on the third day. Voiding was satisfactory. Distention did not appear. The wound healed per primam, and by the tenth day she was up and about most of the day (Fig. 11, *A* and *B*). Three weeks after operation she walked out of the hospital to her car to begin a 1,800 mile trip as a passenger.

She did well at home until she was abruptly taken severely ill on April 1, 1948. She developed deep jaundice, became comatose, and died on April 10, 1948. No autopsy was obtained. It seems highly probable that she died of homologous serum hepatitis developed as a sequel to the blood transfusions received during operation.

Summary.—A 50-year-old housewife was subjected to hemipelvectomy for an osteogenic sarcoma of the upper thigh which had caused symptoms for eight months. She was ambulant on the second day. The wound healed per primam and recovery was rapid. She died, apparently of homologous serum jaundice, three months after operation.

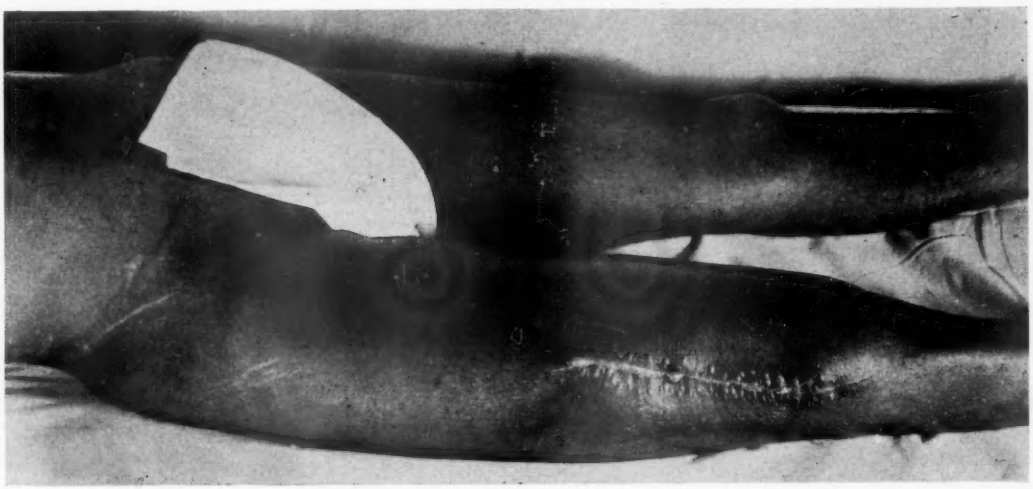
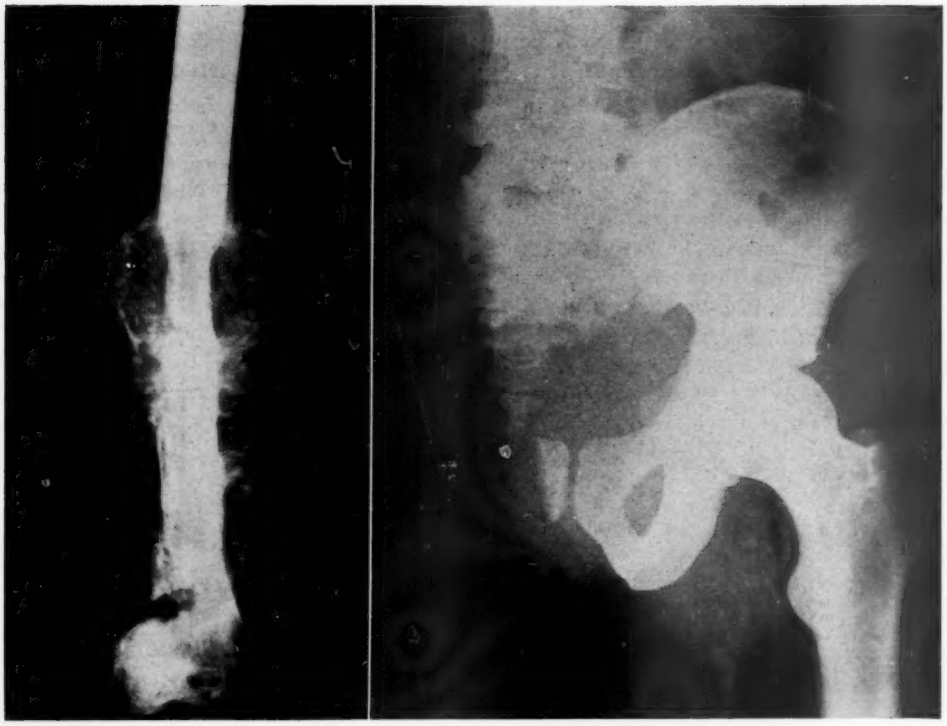


Fig. 12 (Case 3).—O. P. M. (J.H.H. 427065). Osteogenic sarcoma. Preoperative appearance showing the great soft tissue swelling reaching the groin, although the primary osseous involvement (Fig. 14, *A*) is much lower.

CASE 3 (427065).—O. P. M. was a 30-year-old Negro man. He was first seen in June, 1947, complaining of pain and swelling in the lower right thigh of nine months' duration.

A biopsy was performed at another hospital in February, 1947, and reported to show "callus." In March, 1947, he had fallen, injuring the swollen area. The swelling and pain increased. Roentgen films in June, 1947, showed an area of destruction on the anterior and lateral aspect of the lower third of the femur with bone proliferation about the femur. The lesion was suspected of being a sarcoma but a chronic nonsuppurative osteomyelitis seemed a reasonable possibility. In July, 1947, the femur was explored. The cortex was hard, the medullary cavity was small, and at the distal end of the femur was what appeared to be a large soft callus. Microscopic study showed bone formation from osteoid tissue and it was felt that this represented callus and neither tumor nor infection. The wound healed well and he was discharged diagnosed as having chronic sclerosing osteomyelitis. The callus was presumed to be the result of the previous biopsy.

In October, 1947, at another hospital the tumor was excised, so much of the thickness of the femur being resected that in December, 1947, an iliac bone graft was performed. He remained in that hospital until March, 1948, when he returned to the Johns Hopkins Hospital.



A. *B.*

Fig. 13 (Case 3).—*A.* Preoperative roentgenogram. Note the extent of the tumor and the peculiar globelike tumor masses. *B,* Postoperative roentgenogram.

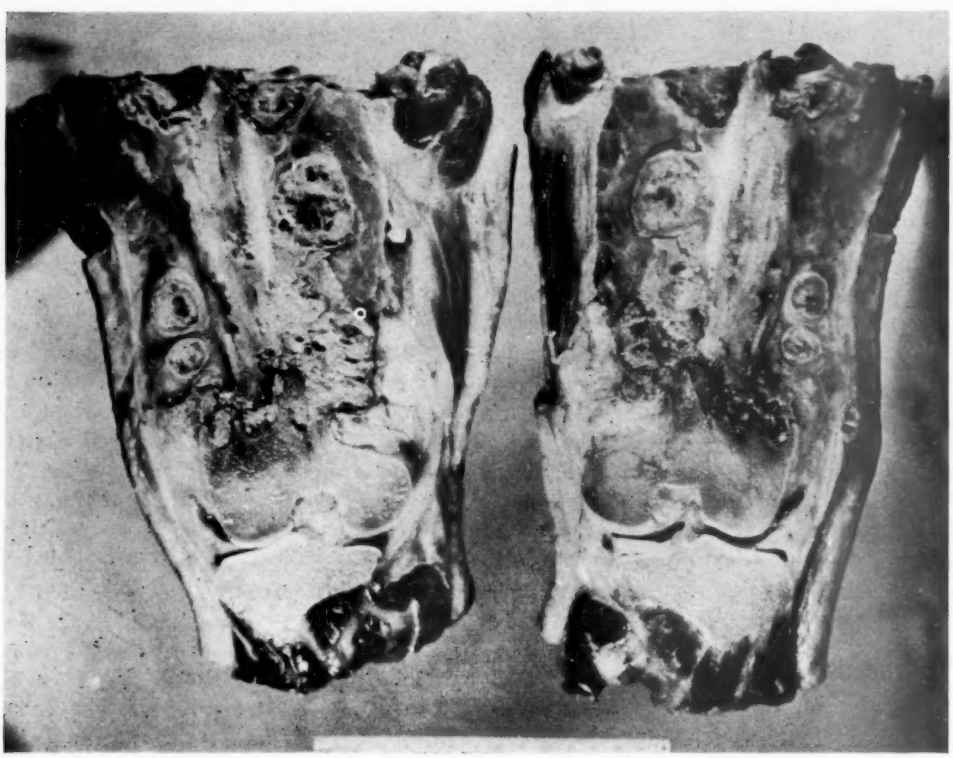
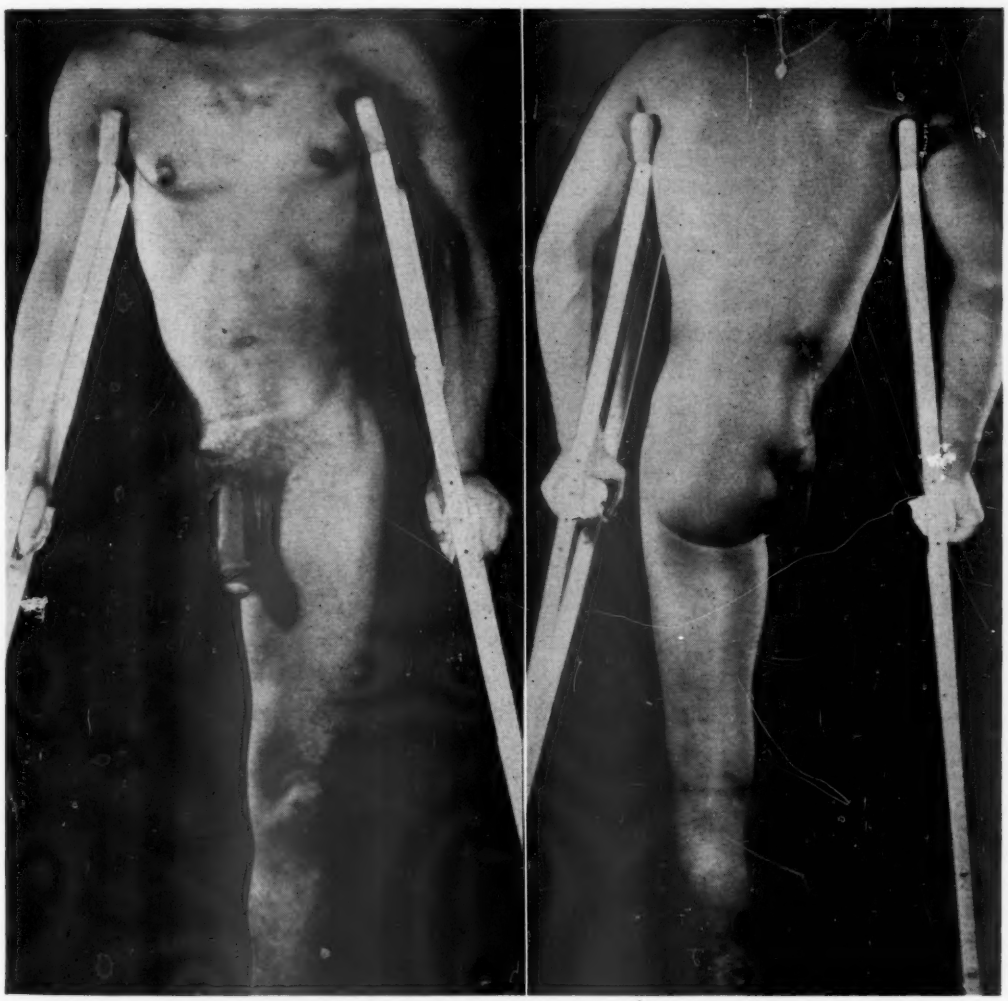


Fig. 14 (Case 3).—Frontal section of the lower portion of the specimen showing the complete destruction of the femur and the peculiar globelike metastases in the near-by soft tissues.

General physical examination was negative except for the right lower extremity. There was a great swelling of the right thigh, hard and fixed to the skin, which was adherent from the knee to the upper thigh (Fig. 12). The swelling surrounded the limb and the thigh from knee to groin, was hot, greatly swollen, and extremely tender. There was marked limitation of motion of the knee. Radiographic examination showed an extensive destructive process involving the entire distal half of the right femur (Fig. 13, *A*). This lesion had destroyed most of the cortex of the bone and extended out into the soft tissue. The femoral shaft in its midportion was surrounded by a large mass with a calcified rim. There were numerous peculiar discrete nodular calcified shadows in the soft tissues. There was no evidence of distant metastasis. The long history suggested a sarcoma developing in a benign lesion, probably Garré's sclerosing osteomyelitis.



A. *B.*

Fig. 15, *A* and *B* (Case 3).—Photographs taken in the outpatient department three weeks after operation.

A biopsy on April 1, 1948, showed a friable, gray, cartilaginous tumor containing spicules of bone. Microscopic sections showed a very cellular tumor composed of spindle cells with large hyperchromatic nuclei. The tumor cells appeared to be forming osteoid tissue in some areas, spicules of bone in others. The tumor was considered to be an osteogenic sarcoma.

The diagnosis of sarcoma being established, a hemipelvectomy was decided upon because of the extensive involvement of the soft tissues. No amputation was feasible at a level permitting the use of a prosthesis. Even a disarticulation of the hip would have meant transecting muscles and fascial planes only a few inches above the tumor.

On April 6, 1948, a right hemipelvectomy was performed. The operation took two hours and was well tolerated. He received 2,000 c.c. of blood during the procedure.

Pathologic Report.—There were numerous enlarged inguinal nodes which did not contain tumor. There was a long scar extending 18 cm. up from the knee with at least one palpable nodule, 0.5 cm. in diameter, in the scar. This nodule was a discrete encapsulated sphere of tumor. Twenty-two centimeters above the knee a cross section showed no gross tumor, but tremendous edema of muscles and subcutaneous tissue. Just distal to this was the main tumor mass, which seemed encapsulated except anteriorly, the capsule being a thin shell of bone. A remarkable feature was the presence of several round tumor nodules 1 to 4 cm. in diameter in the soft tissues anterior to the principal tumor (Fig. 14). The sections of the skin showed tumor nodules in the corium. In general, the tumor was an osteogenic sarcoma, as seen in the biopsy sections.

On the day following the operation he was up on crutches and his general condition was good. The wound healed per primam and he left the hospital on April 22, sixteen days after operation (Fig. 15). Hemoglobin was 12.5 Gm. before operation, 10.5 Gm. the day after operation, and 9.8 Gm. one week later.

Summary.—A 30-year-old Negro man developed osteogenic sarcoma in the femur after several previous biopsies and roentgenograms had shown what appeared to be a benign lesion. This may represent sarcoma developing in Garré's sclerosing osteomyelitis. He was out of bed on crutches the day after hemipelvectomy, and the wound healed per primam. He left the hospital on the sixteenth day after operation. He is well five months later except for diminution in sexual power.

CASE 4 (A-64534).—T. J. was a 12-day-old white male. He was born with an extraordinary lymphangioma and hemangioma deforming the entire left lower extremity and invading the pelvis and buttock. A hemipelvectomy was successfully performed and is being reported in detail elsewhere.

SUMMARY

1. Hemipelvectomy is the only effective means of removing malignant tumors of the pelvic girdle and offers a wider margin of safety in the amputation treatment of malignant tumors high in the thigh.

2. The operative technique is described. The operation is not unduly complicated and the present-day mortality is low.

3. Four patients, 12 days to 50 years in age, are reported. Two operations were performed for osteogenic sarcoma and one each for Marjolin's ulcer and for extensive congenital angiomas.

REFERENCES

1. Gordon-Taylor, G.: Presidential Address on Amputation, Tr. M. Soc. London (1940-1943) **63:** 143-167, 1945.
2. Leighton, W. E.: Interpelvi-abdominal Amputation, Arch. Surg. **45:** 913-925, 1942.
3. Löffler, quoted by Rudolph Klapp in Bier, Braun, Kümmell: Chirurgische Operationslehre, vol. 5, Leipzig, 1933, Johann Ambrosius Barth, p. 300.
4. Morton, J.: Interinnomino-abdominal (hindquarter) Amputation, Ann. Surg. **115:** 628-646, 1942.
5. Pack, G. T., and Ehrlich, H. E.: Sacroiliac Disarticulation (Hemipelvectomy), Ann. Surg. **124:** 22-48, 1946.
6. Pack, G. T., Ehrlich, H. E., and Gentil, F. de C.: Radical Amputations of the Extremities in the Treatment of Cancer, Surg., Gynec. & Obst. **84:** 1105-1116, 1947.
7. Sugarbaker, E. D., and Ackerman, L. V.: Disarticulation of the Innominate Bone for Malignant Tumors of the Pelvic Parietes and Upper Thigh, Surg., Gynec. & Obst. **81:** 36-52, 1945.

SULFAMETHAZINE IN THE TREATMENT OF URINARY INFECTIONS DUE TO GRAM-NEGATIVE BACILLI

ALEXANDER M. RUTENBURG, M.D., AND FRITZ B. SCHWEINBURG, M.D.
BOSTON, MASS.

(From the Kirstein Laboratory for Surgical Research, Beth Isreal Hospital and the Department of Surgery, Harvard Medical School)

THE antibiotics in common use often fail to exert a sufficient therapeutic effect in urinary infections due to gram-negative bacilli particularly in the case of *Bacillus proteus* and *Bacillus pyocyaneus*. Such failure is due to primary or acquired bacterial resistance[1, 2] or less often to toxic reaction to the drug. In this report we are presenting clinical evidence that sulfamethazine is in certain circumstances superior to other chemotherapeutic agents for the treatment of urinary infection due to gram-negative bacilli.

Our attention was drawn to sulfamethazine (2-sulfanilamido-4,6-dimethyl pyrimidine or dimethyl sulfadiazine) by reports of its high chemotherapeutic potency in vitro, and in vivo in laboratory animals against gram-negative organisms.[3, 4] Clinical trials with this drug (hereafter referred to as SMT) have been limited primarily to the treatment of coccal infections such as lobar pneumonia, pneumococcal meningitis, and gonorrhea.[5-14] The therapeutic results in over 500 patients, of whom close to 400 had lobar pneumonia, were very satisfactory and compared favorably with results achieved with sulfadiazine and sulfamerazine.

Sulfamethazine, given orally in its free form, is absorbed rapidly from the alimentary tract. The maximum concentration in the blood is attained within two to four hours[15, 16] but there is considerable variability in the blood concentration from patient to patient with the same doses.[7, 10, 11, 16, 17] It is, therefore, important to determine blood concentrations during the course of treatment and adjust dosage accordingly. In any given patient on divided daily dosage, however, blood levels can be maintained fairly constant.

The rate of excretion is approximately the same as that of sulfadiazine (SD)[11, 16] and 40 to 80 per cent of the drug appears in the urine as the acetyl derivative.[11, 15, 16] SMT and acetyl SMT are four to five times more soluble than SD and its conjugated form in urine at pH 5.5. Alkalinization of the urine increases the solubility of SMT an additional threefold and of its acetyl derivative 3.5 fold.[16, 18] Since the renal toxicity of a sulfonamide is said to be directly related to its solubility in the urine,[19] SMT may be expected to have the least renal toxicity of all the sulfonamides so far investigated. In experiments with mice, dogs, and monkeys, no renal complications were encountered[19, 17] after prolonged administration of large doses of SMT daily. In man the incidence of toxic reactions during sulfamethazine therapy was approximately 5 per cent. These consisted of rash, vomiting, and transient leuco-

Acknowledgment is due to Dr. Morris Abrams for assistance in the treatment of these patients and to Miss Sunya Gordon for technical assistance.

Acknowledgment is also due to the Lederle Laboratories for supplying the Sulfamethazine.

Received for publication, Oct. 18, 1948.

TABLE I

CASE NO.	PRIMARY DIAGNOSIS	ORGANISMS PRESENT BEFORE TREATMENT	ORGANISMS PRESENT AFTER TREATMENT	CLINICAL RESULT	SULFAMETHAZINE DOSAGE GM. PER DAY	SULFAMETHAZINE DAYS	(SMT) BLOOD LEVEL	RESPONSE I	RESPONSE II	RESPONSE III	REMARKS
1	Cystitis, acute	Esch. coli	None	Excellent	4-6	6	13	x			
2	Cystitis, acute	Esch. coli	None	Excellent	6	5	14.4	x			
3	Cystitis, postoperative	Esch. coli	Esch. coli	Poor	6	9	6.5-12.2			x	Rash
4	Cystitis, acute, urinary tb. with secondary invaders	Esch. coli	None	Excellent	4	15	--	x			No tubercle bacilli found in urine
5	Cystitis, postoperative	Esch. coli	None	Excellent	4	5	±	x			SMT blood concentration too low to be measured
6	Cystitis, postoperative	A. aerogenes	A. aerogenes	Improved	6	13	5.6		x		
7	Cystitis, postoperative	A. aerogenes	A. aerogenes	Improved	6	6	7.3-10.2		x		
8	Cystitis, acute	B. proteus	None	Excellent	4	4	4.5	x			
9	Benign prostatic hypertrophy, suprapubic prostatectomy	Esch. coli, B. proteus, A. aerogenes, B. pyocyaneus	Esch. coli (little), Str. faecalis	Excellent	4	8	5.0		x	•	Streptomycin prior to SMT; toxic reaction
10	Cystitis, postoperative	Esch. coli, B. pyocyaneus, A. aerogenes, Str. faecalis	Esch. coli, B. pyocyaneus, Str. faecalis	Improved	6	28	1.7- 1.9		x		
11	Benign prostatic hypertrophy, suprapubic prostatectomy	Esch. coli, B. pyocyaneus, A. aerogenes, B. proteus	B. pyocyaneus (little)	Excellent	4	26	2.0		x		SD, ST, organisms resistant; toxic reactions to both drugs
12	Cystitis, secondary to urethral stricture	B. proteus, B. pyocyaneus	B. pyocyaneus	Excellent	6	4	7.0		x		SD, ST, Streptomycin, organisms resistant, toxic reactions to all 3 drugs

13	Benign prostatic hypertrophy, suprapubic prostatectomy	Esch. coli, B. pyocyaneus hemolytic str.	B. pyocyaneus	Excellent	4-6	13	3.1-11.0	x		SD, ST; toxic reactions
14	Cystitis, following prostatectomy	Pneumococcus, B. pyocyaneus heavy	B. pyocyaneus (1 colony)	Excellent	6	5	13.6-25.9	x		Transient leucopenia
15	Benign prostatic hypertrophy, suprapubic prostatectomy	Esch. coli, A. aerogenes, B. pyocyaneus	B. pyocyaneus	Excellent	6	9	0.3	x		SD, ST organisms resistant
16	Cystitis, chronic hemorrhagic	Esch. coli, A. aerogenes	Esch. coli, A. aerogenes	Improved	6	11	4.3- 4.7		x	SD, ST; toxic reactions
17	Interstitial intractable cystitis, bilateral nephrostomy	Esch. coli, B. pyocyaneus, Staph. aureus* Str. viridans	Esch. coli, B. pyocyaneus Str. viridans	Poor	4	7	27.3 2.7- 6.9		x	ST, SD organisms resistant
18	Cystitis, postoperative	Esch. coli, B. pyocyaneus	Esch. coli	Poor	6	7	5.2- 6.1	x		SD, ST organisms resistant, toxic reactions
19	Cystitis, following prostatectomy	B. pyocyaneus B. proteus, A. aerogenes. nonhemolytic str. Staph. aureus	None	Excellent	6	18	2.4- 6.9	x		SD, ST organisms resistant
20	Cystitis, urethral stricture	Esch. coli, B. proteus, non-hemolytic str.	B. proteus, Non-hemolytic str.	Improved	4	11		x		SD, ST organisms resistant, toxic reactions to both drugs
21	Benign prostatic hypertrophy, retropubic prostatectomy	A. aerogenes, B. pyocyaneus, Str. faecalis	None	Excellent	4	14	±	x		SD, sulfamerazine organisms resistant
22	Cystitis, postoperative	B. proteus, A. aerogenes	None	Excellent	4	8	6.5	x		SD, ST organisms resistant
23	Cystitis, postoperative	Esch. coli, A. aerogenes	Esch. coli (6 colonies)	Excellent	6	3½	3.1	x		
24	Cystitis, postoperative	B. pyocyaneus, A. aerogenes	None	Excellent	4	8	±	x		

*Three colonies of Staph. aureus found only in first urine specimen.

penia.[5-14] No serious reactions were encountered and there were no instances of renal damage. Only two patients were reported to have crystalluria; one of them also had hematuria.[11]

This report deals with the results of sulfamethazine therapy in twenty-four unselected patients with a variety of urinary tract infections (Table I). All patients had pyuria and positive urine cultures. Frequency, dysuria, fever, and leucocytosis were among the most frequently noted clinical symptoms and signs. Eleven patients had prior treatment with other sulfonamides and either failed to respond or had toxic reactions. Sixteen patients received penicillin and five streptomycin in adequate dosage without a therapeutic effect before sulfamethazine was given. Sixteen patients were either on constant drainage or were subjected to repeated catheterization for urinary retention. Obstructive pathology in the urinary tract, if present, was treated during SMT therapy.

Four to six grams of SMT were given in divided doses together with 2 to 2½ liters of fluid daily. $NaHCO_3$, 15 to 20 Gm., was also given daily in order to shift the urinary pH as far as possible toward the alkaline side. Even with this dose of alkali the pH ranged between 6 and 7.5. Most of the patients were treated for five to fifteen days (Table I). The duration of treatment was based upon the clinical and bacteriologic response.

The urine specimens for culture were obtained by catheterization in all females and in most males. In a few instances a "clean voided" specimen was obtained in male patients. Cultures were taken at intervals ranging from one to three days and were repeated about once a week after termination of treatment. Thereafter, follow-up studies were carried out on the patients for periods ranging from two to ten weeks. In planting the urine cultures the same sized loop was used in all cases. One loop was streaked over the surface of blood agar, agar, and endo plates. The plates were observed for forty-eight hours.

While the patients were on SMT medication the urine was frequently examined for blood, pus, and sulfamethazine crystals. The pH was determined daily.

RESULTS

The results were evaluated on a clinical and bacteriologic basis and are summarized in Table I. The clinical response is indicated by excellent, if all symptoms disappeared; by improved, if most but not all clinical complaints disappeared; and by poor, if there was no clinical improvement. Bacteriologically the results are classified by the following types of response:

I. Sterile urine

II. In cases with mixed infection, of the several bacterial strains present, some were completely removed, while the count of the remainder was markedly reduced

III. No change in the bacteriologic findings

Of twenty-four patients who received sulfamethazine, nine had Response I, ten had Response II, and five patients had Response III. The types of response under each primary diagnosis are summarized in Table II.

TABLE II. RESULTS OF SULFAMETHAZINE TREATMENT IN RELATION TO DIAGNOSIS

PRIMARY DIAGNOSIS	TOTAL CASES	RESPONSE*			TOTAL FAVORABLE RESPONSES
		I	II	III	
Benign prostatic hypertrophy, suprapubic prostatectomy	5	1	4	0	5
Cystitis, secondary to operation	9	3	3	3	6
Cystitis, secondary to urethral stricture	2	0	2	0	2
Acute cystitis	3	3	0	0	3
Chronic hemorrhagic cystitis	1	0	0	1	0
Chronic cystitis secondary to prostatectomy	2	1	1	0	2
Urinary tract tuberculosis with secondary infection	1	1	0	0	1
Interstitial intractable cystitis, bilateral nephrostomy	1	0	0	1	0
Total	24	9	10	5	19

*See text.

In patients with a II or III response, the persisting organisms were tested for in vitro sensitivity to SMT and were found to be resistant. The same bacteria were also found to be resistant to SD and sulfathiazole (ST). Occasionally strains of organisms resistant to SD and ST were sensitive to SMT. The effects of treatment on the individual bacterial strains are summarized in Table III.

TABLE III. RESULTS OF SULFAMETHAZINE TREATMENT ON INDIVIDUAL ORGANISMS

UNIVALENT INFECTIONS

BACTERIA	TOTAL NUMBER OF CASES	NUMBER OF CASES CLEARED	NUMBER OF CASES NOT CLEARED
Esch. coli	5	4	1
A. aerogenes	2	0	2
B. proteus	1	1	0

MIXED INFECTIONS

BACTERIA	TOTAL NUMBER OF CASES	CASES IN WHICH BACTERIA WERE REMOVED	CASES IN WHICH BACTERIA WERE NOT REMOVED
Esch. coli	10	4	6
A. aerogenes	10	9	1
B. pyocyaneus	12	5	7
B. proteus	5	4	1
Staph. aureus	2	2	0
Hemolytic str.	1	1	0
Str. viridans	1	0	1
Nonhemolytic str.	2	1	1
Str. faecalis	3	1	2
Pneumococcus	1	1	0

Of the eight cases with univalent infections there were three failures (two *Aerobacter aerogenes* and one *Escherichia coli*) due to bacterial resistance.

Of the sixteen patients with mixed infections, two patients showed no bacteriologic response, but one of them (Case 14) showed clinical improvement. Of the remaining fourteen patients, four were cleared and ten showed definite bacteriologic improvement. In one of these patients (Case 18), with postoperative cystitis due to *Esch. coli* and *B. pyocyaneus, B. pyocyaneus* was cleared from the urine and *Esch. coli* decreased in number but there was no clinical response. This patient subsequently responded to streptomycin. The clinical results were satisfactory in the other thirteen patients.

Of ten strains of gram-positive cocci (see Table I) found in nine cases of mixed infections, six were removed from the urine in the course of SMT medication. Two strains of *Str. faecalis,* and two strains of nonhemolytic streptococci failed to respond to SMT. Some of these were removed by subsequent treatment with mandelamine. Of the gram-negative bacteria 83 per cent of *B. proteus,* 75 per cent of *A. aerogenes,* 53 per cent of *Esch. coli,* and 42 per cent of *B. pyocaneus* were removed during SMT treatment. Clinically, 88 per cent of all patients treated showed definite improvement.

Two patients had toxic reactions. One patient (Case 14) developed a transient leucopenia. Failure to maintain fluid intake while on SMT medication resulted in a SMT blood level of 25.9 mg. per cent. Following withdrawal of the drug and hydration, the concentration fell to 5.1 mg. in twenty-four hours and the white blood cell count returned to normal within forty-eight hours. Another (Case 16) developed an allergic skin rash following eleven days (66 Gm.) of therapy. Withdrawal of the drug resulted in prompt recovery. This patient was also a bacteriologic failure. The responsible organisms were resistant to SMT, SD, and ST, but were subsequently cleared by an intensive course of streptomycin.

DISCUSSION

Analysis of our results shows that 37.5 per cent of the patients treated were cured and 41.5 per cent were improved both clinically and bacteriologically, indicating a satisfactory response to medication in 79 per cent of the patients. Thirteen patients had no prior medication with other antibiotics; of these forty-six per cent were cured and 31 per cent improved. It is notable that of eleven patients in whom previous treatment with sulfadiazine and sulfathiazole had failed, nine (82 per cent) showed a favorable response to sulfamethazine. Two other patients who had an unsatisfactory result with streptomycin responded favorably to sulfamethazine. These findings also compare favorably with the results reported from the use of other chemotherapeutic agents for similar infections.[2, 20-31]

The results of streptomycin therapy in urinary infections due to gram-negative organisms, exclusive of infections in paraplegic patients, are variable. Recent reports indicate this antibiotic to be effective in 23 to 90 per cent of the patients treated.[20-25] Streptomycin failures were attributed to bacterial resistance, which tends to develop rapidly, and to toxic reactions which have been reported to have an incidence up to 25 per cent.[24] Inconvenience of administration and financial considerations are further disadvantages of streptomycin therapy.

Sulfadiazine therapy has been widely applied and has been beneficial in 57 to 74 per cent of the patients treated.[26, 27, 28] Patients with a single bacterial organism in the urine responded better than those with mixed infections. In the patients treated with SMT there was an equally favorable response in both types of infection.

Sulfathiazole has been efficacious in 65 per cent of patients with urinary infections.[28, 29, 30] Nu-445 (3,4-dimethyl-5-sulfanilamido-isoxazole), desirable be-

cause of its high degree of solubility and low toxicity, was effective in 36 per cent of patients with infections caused by *B. proteus* and *Esch. coli.*[31*] Sulfathalidine, although reported to be highly effective (86 per cent), apparently is of value only against *Esch. coli.*[32]

SMT has a lower incidence of systemic toxicity and of renal toxicity than SD or ST. In the series of patients reported here no instances of crystalluria, hematuria, or azotemia developed as a sequel to its use.

In two patients in whom the blood concentration of SMT was in excess of 25 mg. per cent and urinary pH was acid, SMT crystals were not found in the urinary sediment.

SUMMARY

The results of treatment of twenty-four patients with urinary tract infections caused by gram-negative bacilli are described. Of the patients treated, 79 per cent showed a favorable response.

The clinical and bacteriologic results observed with SMT compare well with the most favorable results obtained with other drugs. The lack of renal toxicity and the low incidence of systemic reactions are notable. Furthermore, SMT has been used successfully in some cases in which SD and ST and streptomycin had failed or where treatment had to be discontinued because of toxic reactions. Penicillin, as is well known, has no effect on gram-negative bacilli.

In two of the failures the organisms found to be resistant to SMT responded subsequently to streptomycin and in another to mandelamine (Str. faecalis). In vitro sensitivity tests were used as a basis for the choice of the most suitable drug.

CONCLUSION

Sulfamethazine is a valuable addition to the list of chemotherapeutic agents for urinary infections due to gram-negative organisms because of its extremely low renal toxicity and its effectiveness, not only when used as the initial drug in the treatment but also after others have failed to control the infection.

REFERENCES

1. Finland, M., Murray, R., Harris, H. W., Kilham, L., and Meads, M.: Development of Streptomycin Resistance During Treatment, J. A. M. A. **132:** 16-21, 1946.
2. Pool, T. L., and Cook, E. N.: Present Concepts of Treatment of Infections of the Urinary Tract, J. A. M. A. **133:** 584-587, 1947.
3. Schweinburg, F. B., and Yetwin, I. J.: Sulfamethazine; In Vitro Action on Enteric Pathogens as Compared With Sulfadiazine and Sulfamerazine, J. Bact. **49:** 193-197, 1945.
4. Schmidt, L. H., Sesler, C. L., and Hughes, H. B.: The Chemotherapeutic Activities of Sulfamerazine and Sulfamethazine, J. Pharmacol. & Exper. Therap. **81:** 43-57, 1944.
5. Loughlin, E. H., Bennett, R. H., and Flanagan, M. E.: Treatment of Pneumococcal Pneumonia With Sulfamethazine, J. Lab. & Clin. Med. **29:** 568-573, 1944.
6. Morgan, T. N., and Wylie-Smith, R.: Lobar Pneumonia Treated With Sulphamezathine and Sulphadiazine, Lancet **2:** 731-733, 1943.
7. Milton, G.: Sulphamezathine in Lobar Pneumonia. A Comparison With Sulphapyridine, Lancet **1:** 277-278, 1944.
8. Pakenham-Walsh R.: Pneumococcal Meningitis—Recovery With Sulfamethazine, Lancet **1:** 649, 1943.

*The results of treatment with this drug in twenty patients in this hospital were much less satisfactory than our results with sulfamethazine. (To be published.)

9. Johnson, A. G.: Sulphamezathine in Gonorrhea in the Male, Brit. J. Ven. Dis. **20**: 31-33, 1944.
10. Dowling, H. F.: New Chemotherapeutic Agents in Treatment of Infectious Diseases —Sulfamerazine and Sulfamethazine, M. Ann. District of Columbia **12**: 468-471, 1943.
11. McDermott, W., Gilligan, D. R., Wheeler, C., and Plummer, N.: Clinical Studies of Sulfamethazine, New York State J. Med. **44**: 394-397, 1944.
12. Bullowa, J., and Ratish, H. D.: A Therapeutic and Pharmacological Study of Sulfadiazine, Sulfamerazine, and Sulfamethazine in Lobar Pneumonia, J. Clin. Investigation **23**: 676-681, 1944.
13. Macartney, D. W., Luxton, R. W., Smith, G. S., Ramsay, W. A., and Goldman, J.: Sulphamethazine, Clinical Trial of New Sulphonamide, Lancet **1**: 639-641, 1942.
14. Jennings, P. A., and Patterson, W. H.: Sulphamethazine—Clinical Trial in Children, Lancet **2**: 308-309, 1942.
15. Clark, J. K., Murphy, F. D., and Flippin, H. F.: Absorption, Excretion and Distribution of Sulfamethazine in Man, J. Lab. & Clin. Med. **28**: 1828-1834, 1943.
16. Volini, I. F., Engbring, G. M., and Schorsch, H. A.: Absorption, Excretion and Distribution of Sulfamethazine, Arch. Int. Med. **75**: 168-174, 1945.
17. Rose, F. L., Martin, A. R., and Bevan, H. G. L.: Sulphamethazine (2,4'-Aminobenzenesulphonyl-amino -4:6-dimethyl pyrimidine): New Heterocyclic Derivative of Sulfanilamide, J. Pharmacol. & Exper. Therap. **77**: 127-144, 1943.
18. Gilligan, D. R., and Plummer, N.: Comparative Solubilities of Sulfadiazine, Sulfamerazine, and Sulfamethazine, and Their N_4 -acetyl derivatives at Varying pH Levels, Proc. Soc. Exper. Boil. & Med. **53**: 142-145, 1943.
19. Schmidt, L. H., Hughes, H. B., Badger, E. A., and Schmidt, I. G.: The Toxicity of Sulfamerazine and Sulfamethazine, J. Pharmacol. & Exper. Therap. **81**: 17-42, 1944.
20. Lazarus, J. A., Marks, M. S., and Schwarz, L. H.: Pyocaneus Infections of the Urogenital Tract With Special Reference to Streptomycin Therapy, J. Urol. **59**: 243-251, 1948.
21. Furguson, C., and Hershey, T. H.: Streptomycin in Genitourinary Infections, J. Urol. **57**: 932-937, 1947.
22. Adcock, J. D., and Plumb, R. T.: Streptomycin for Urinary Tract Infections, J. A. M. A. **133**: 579-584, 1947.
23. Pulaski, E. J.: Streptomycin in Surgical Infections; Infections of the Genito-Urinary Tract, Ann. Surg. **124**: 392-401, 1946.
24. Bandler, C. G., Roen, P. R., and Mulaine, V. J.: Streptomycin in Genito-Urinary Infections, J. Urol. **59**: 96-110, 1948.
25. Garvey, F. K., and Canning, T. E.: Streptomycin in Urinary Infections, J. Urol. **60**: 176-186, 1948.
26. LaTowsky, L. W.: The Clinical Use of Sulfadiazine in Non-specific Urinary Tract Infections—A Study of 100 Cases, J. Urol. **50**: 625-631, 1943.
27. Satterthwaite, R. W., Hill, J. H., and Young, H. H.: The Use of Sulfadiazine in Urinary Tract Infections and Gonorrhea and as a Prophylactic to Prevent Postoperative Infections, J. Urol. **46**: 101-109, 1941.
28. Helmholz, H. F.: Bacteriostatic Action of Sulfadiazine, Sulfathiazole, Sulfacetamide, and Sulfapyridine in Bacteria Isolated from Urinary Infections, Proc. Staff Meet., Mayo Clin. **17**: 529-533, 1942.
29. Culp, O. S.: Sulfathiazole Treatment of Urinary Tract Infections, J. Urol. **44**: 116-124, 1940.
30. Alyea, E. P.: Sulfathiazole Therapy in Urinary Tract Infections, J. Urol. **47**: 219-223, 1942.
31. Narins, L.: The Treatment of B. Coli and B. Proteus Infections of the Urinary Tract With a New Sulfonamide (Nu-445), J. Urol. **59**: 92-95, 1948.
32. Everett, H. S., Vosberg, G. A., and Davis, J. M.: The Treatment of E. Coli Infections With Sulfathalidine (phthalylsulfathiazole), J. Urol. **59**: 83-90, 1948.

MECONIUM PERITONITIS

J. Richmond Low, M.D., Princeton, W. Va., George Cooper, Jr., M.D., and Lewis Cosby, Jr., M.D., Charlottesville, Va.

(From the Departments of Surgery and Gynecology, Radiology, and Pediatrics of the University of Virginia Hospital, Charlottesville, Va.)

MECONIUM peritonitis is a sterile reaction in the peritoneum of the newborn infant resulting from the escape of intestinal content. It is an uncommon condition which is not too well understood and which is believed to result from a number of different causes. Most reports in the literature are those of autopsies, and the number of proved cases with patients surviving is small. We wish to report one patient with meconium peritonitis with an associated atresia of the terminal ileum who was operated upon and survived.

In 1838 Simpson[1] published his observations on this condition with a review of the literature, comprising 25 cases. Rudnew,[2] in 1915, reported a series of 40 cases. According to Abt[3] 60 additional cases were reported up to 1924. In all, a few more than 100 cases have been reported to date.

Meconium peritonitis of the newborn infant is a pathologic entity completely different from acute bacterial peritonitis. It is an aseptic chemical peritonitis caused by the entrance of meconium into the peritoneal cavity through a perforation of the intestinal tract. This peritonitis occurs during intrauterine life, at the time of birth, or immediately after birth. The perforation is thought to occur some time after the fourth or fifth month of fetal life. Meconium is a sterile mixture of bile, cast-off epithelial cells, swallowed liquor amnii, pancreatic, gastric, and intestinal secretions. Peristalsis, which probably begins early in fetal life, would appear to be necessary to cause rupture of the intestine.

Analysis of the cases reported by Rudnew[2] shows that approximately 50 per cent are associated with demonstrable intestinal obstruction of one sort or another, ranging from developmental intestinal atresia through common adult causes such as adhesions, volvulus, and intussusception. In these cases the mechanism of meconium peritonitis is fairly clear. Meconium within the intestinal lumen is thought to stimulate peristalsis, which when working against an obstruction causes a perforation of the bowel wall with extrusion of the meconium into the free peritoneal cavity. "Meconium ileus" was thought by Landsteiner[4] to be a frequent cause of perforation of the bowel. This disease is associated with fibrosis of the pancreas and absence or diminution of pancreatic secretion. Lacking this secretion, the meconium within the bowel becomes puttylike and adherent to the bowel wall so that it cannot be propelled along the gastrointestinal tract. This may set up an obstruction to the lumen of the bowel and perforation may occur proximal to it.

Whatever the cause, the perforation of the bowel usually closes prenatally and frequently the site of perforation is not found at operation or at autopsy.

Received for publication, Dec. 16, 1948.

The peritoneal reaction is that of a chemical or foreign body peritonitis with meconium deposits, the formation of dense adhesions, agglutination of loops of bowel, and calcification.

Of the other 50 per cent of cases in which meconium peritonitis exists without demonstrable organic obstruction, many causes have been listed. Trauma was considered of the utmost importance by Zillner.[5] Ulcers of the bowel, Meckel's diverticulum, the appendix, and other congenital diverticula are the sites of perforation. Still other cases of meconium peritonitis have been described, one by Boikan,[6] in which there is no satisfactory explanation for the perforation.

Many of these children are born dead or die soon after birth. Those who survive present a picture of intestinal obstruction.

In 1944 Neuhauser[7] reported three cases from the Children's Hospital in Boston in which it was possible to make the diagnosis preoperatively by means of x-ray examination. The diagnosis in the case to be reported was also made preoperatively by x-ray examination. In addition to the picture of intestinal obstruction, x-ray examination showed scattered calcifications in the peritoneal cavity. Litten[8] felt that calcification may occur as early as twenty-four hours after the onset of the peritonitis. In neonatal intestinal obstruction the presence of shadows of calcium density in the abdomen should make the diagnosis frequently possible.

CASE REPORT

J. H. C., a 4-day-old white male weighing 7 pounds, 1¾ ounces, was admitted Feb. 17, 1948, with a diagnosis of intestinal obstruction. This was the first child of a 21-year-old mother, born as a breech presentation after a normal full-term pregnancy and labor of twelve hours' duration. The birth weight was 8 pounds, 5 ounces and the condition was said to be good. The child vomited shortly after the first feeding and continued to vomit periodically until admission to this hospital. Vomitus was sometimes black and sometimes dark greenish. He passed one stool, the character of which was not known. Several enemas were given but were ineffectual. The abdomen became increasingly distended and the child's condition deteriorated rapidly.

Physical examination on admission revealed an acutely ill child who was pale, dusky, and lethargic. The skin had lost its turgor, was dry and inelastic. Temperature was 103° F. by rectum, pulse 160, respirations 40. The heart sounds were poor but the lungs were clear. The abdomen was moderately distended, soft, and doughy in consistency. In the right lower quadrant there was a soft, indefinite mass approximately 3 cm. in diameter. On auscultation no peristaltic sounds were heard. Rectal examination was not done.

Laboratory work on admission revealed a hemoglobin of 18 Gm., a red blood count of 7.2 million cells, a white blood count of 18,000 with a predominance of granulocytes. Carbon dioxide combining power was 47 volume per cent. Urinalysis was normal except for 25 red cells per high-power field. No stool was obtainable for examination.

An x-ray examination of the abdomen was made on admission and was reported as follows: Abdominal films showed gas in the stomach and small bowel loops in the left upper quadrant only. There were fluid levels in the upright position. Fine calcifications were scattered throughout the abdomen. There were a few linear deposits on the inner surface of both lateral abdominal walls. There was a collection of small deposits in the left side of the pelvis and another large collection in the region of the cecum. Conclusions were intestinal obstruction, proximal to the colon, and meconium peritonitis. The latter is often associated with atresia of the ileum (Fig. 1).

Intravenous fluids were administered and a catheter was passed into the stomach and connected to a continuous suction apparatus. After seven hours of treatment the child's condition had improved considerably and operation was decided upon.

Under light drop ether anesthesia supplemented with continuous oxygen administered through a nasal tube, a right rectus muscle-splitting incision was made and the peritoneum exposed. It was markedly thickened and inflamed and within it areas of calcification were countered. The peritoneal cavity was entered with considerable difficulty because of agglutination of the bowel to the anterior peritoneum (Fig. 2). There appeared to be no free peritoneal space. Everywhere loops of small bowel were agglutinated to one another by vascular adhesions. Immediately beneath the incision there was a dilated loop of small

Fig. 1.—Preoperative x-ray view of the abdomen with the patient upright showing scattered calcium throughout the peritoneum, especially in the right lower quadrant. On this film the diagnosis of meconium peritonitis was made.

bowel approximately 2.5 cm. in diameter and 5 or 6 cm. in length. This loop was dissected out from other loops of more normal-appearing bowel and was found to terminate in a blind pouch. Adjacent to this was found a small, collapsed loop of small bowel approximately 8 mm. in diameter which also ended in a blind loop. This segment of bowel was dissected out and found to enter the cecum approximately 7 cm. distally. The cecum and ascending colon were completely collapsed but appeared to have a lumen. Saline solution was injected into the collapsed terminal ileum until it and the cecum were distended with fluid. It then became apparent that a complete atresia of the terminal ileum existed. Because of the agglutination of the peritoneal contents it was impossible to determine whether this was the only point of atresia. The mesenteries of the two blind loops described were continuous

with each other. The proximal bowel was markedly thickened and friable, but its blood supply seemed adequate. During further freeing of the proximal dilated loop a traumatic perforation occurred at a point where a cordlike adhesion was attached. The bowel at this point was extremely thin, and it was thought that it was probably the point of prenatal perforation and the source of meconium peritonitis. The accidental opening was closed.

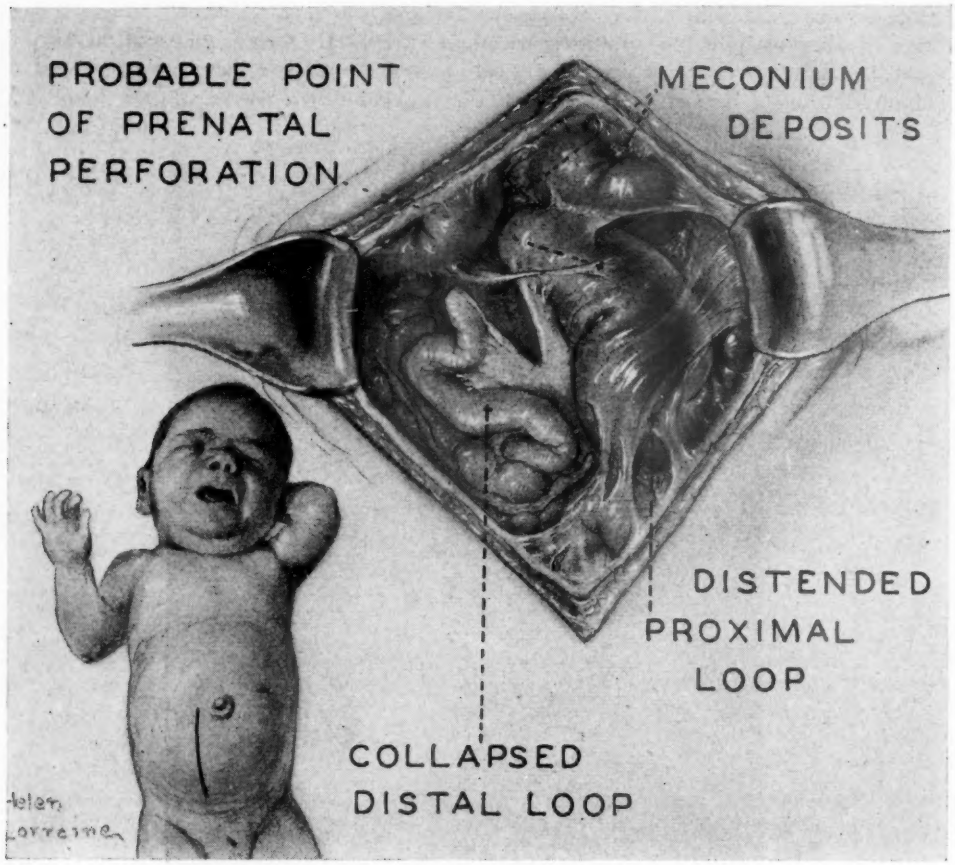


Fig. 2.—Artist's reconstruction of operative findings. Note the two blind ends with enormous distention of the proximal loop.

The two loops were easily brought together side to side in an antiperistaltic manner. An open side-to-side anastomosis approximately 2 cm. in length was performed. After the anastomosis had been completed the distal bowel was again injected with saline solution and fluid was seen to distend the proximal loop. The anastomosis was placed in the peritoneal cavity so that no kinking would occur. Several biopsies of the peritoneum were taken and the wound was closed in layers. One hundred thousand units of penicillin and ½ Gm. streptomycin in solution were placed in the peritoneal cavity in the region of the anastomosis before the peritoneum was closed. During the procedure the child was given two blood transfusions of 60 c.c. each. At the conclusion of the operation the child was extremely pale and cold, and the extremities were blue. He was returned to the bassinet where warmth was applied, duodenal suction was continued, and a slow drip of fluid was administered. He was put in an oxygen tent and given 10,000 units of penicillin and 25 mg. of streptomycin intramuscularly every three hours.

Microscopic examination of the biopsies from the peritoneum showed granulation tissue with marked infiltration by inflammatory cells, chiefly large mononuclear phagocytes, lymph-

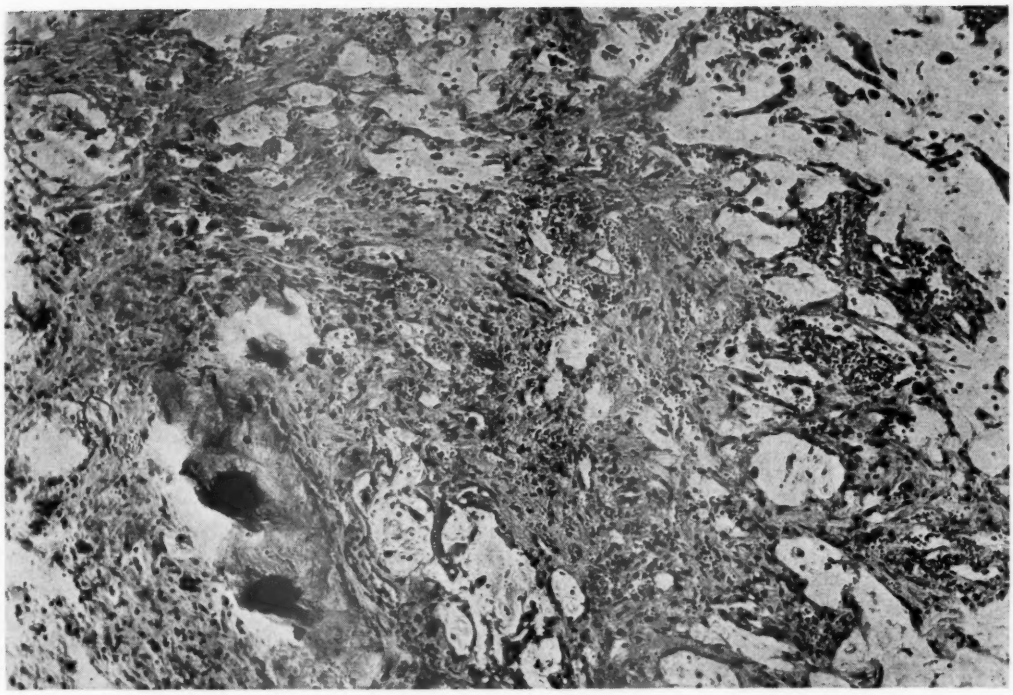


Fig. 3.—Photomicrograph of biopsy from the peritoneum showing marked inflammatory reaction with crystalline deposits and calcium.

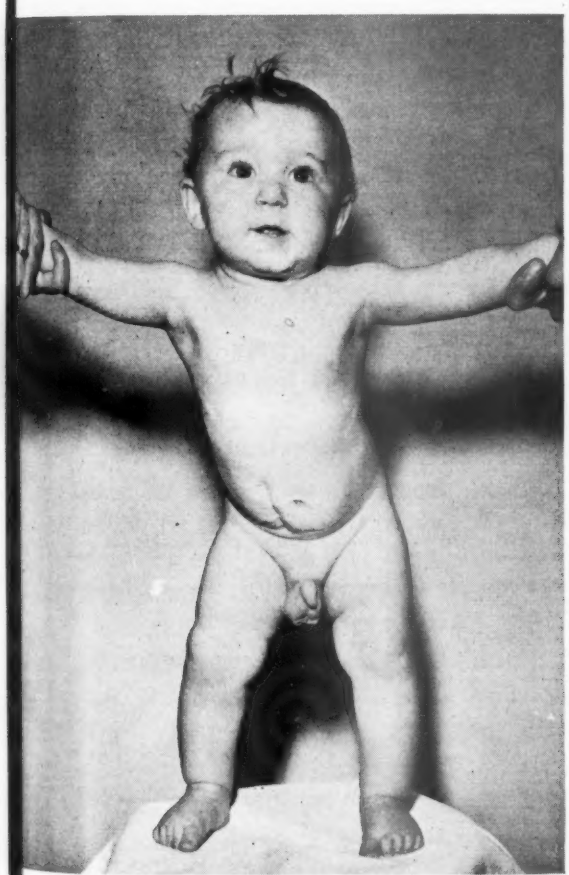


Fig. 4.

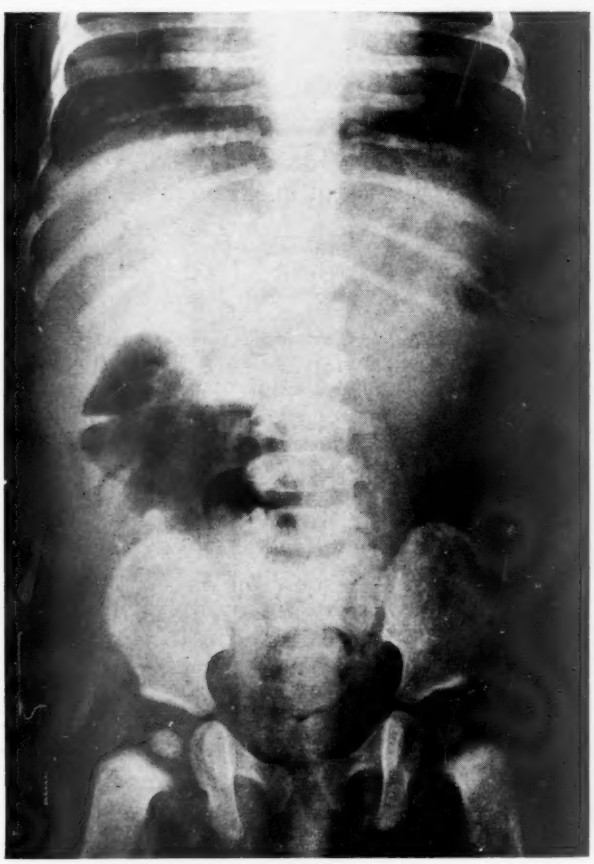


Fig. 5.

Fig. 4.—The patient at 37 weeks showing normal development and nutrition. The small right hydrocele is obvious.

Fig. 5.—X-ray film of the abdomen at 37 weeks showing diminution in the degree of calcium deposit. Compare with Fig. 1.

ocytes, and plasma cells. In some areas there were collections of polymorphonuclear leucocytes. Scattered throughout there were extensive areas of fat necrosis and small areas of calcification (Fig. 3).

Postoperatively the child's condition improved steadily. He was given enemas several times each day to distend the colon and stimulate peristalsis. The abdomen became softer and flatter and peristaltic sounds returned. The suction was discontinued on the third postoperative day, he was given glucose solution by mouth on the fourth postoperative day, and formula on the fifth postoperative day. From that time on he continued to maintain nutrition orally with an occasional supplement of subcutaneous fluid. Stools soon became normal in appearance and frequency. The postoperative course was complicated by a purulent otitis media and a superficial wound infection, both of which responded to treatment. He was discharged from the hospital on March 18, one month after admission.

The patient has been followed in the pediatrics outpatient department, the last visit being Oct. 29, 1948, thirty-seven weeks after birth, and development has been progressive at a normal rate. Weight at 7 weeks was 9 pounds, 7½ ounces, and at 37 weeks 20 pounds, 12 ounces. Except for an occasional stuffy nose the patient has been entirely well. He has had no colic and no vomiting. The bowels have been regular. The diet, which he takes well, included at the time of his last visit, fruits, vegetables, and Pabulum as well as a milk formula. Physical examination revealed a well-developed and well-nourished baby (Fig. 4) who appeared entirely normal. A right hydrocele previously noted was diminishing in size. One observer thought that a little thickening could be felt to the right of the scar in the position of the calcium deposits seen in an earlier x-ray view. It is interesting to note that the flat x-ray film of the abdomen (Fig. 5) revealed marked diminution of the calcium in comparison with earlier films. The baby was to all intents and purposes completely well.

SUMMARY

A case of meconium peritonitis in a 4-day-old infant is reported. The diagnosis was made preoperatively on the x-ray appearance of the abdomen. A successful surgical procedure resulted in apparent complete cure at the age of 37 weeks. At this time the calcium deposits in the peritoneum were disappearing.

REFERENCES

1. Simpson, James Y.: Peritonitis in the Fetus in Uterus, Edinburgh M. J. **15**: 390-414, 1838.
2. Rudnew, W.: Ueber die spontanen Darmrupturen bei Foeten und Neugeborenen, Basel, 1915, Friedrich Reinhardt, 55 pp. 8°.
3. Abt, I. A.: Fetal Peritonitis, M. Clin. North America **15**: 611-622, 1931.
4. Landsteiner, K.: Darmverschluss durch eingedicktes Meconium. Pankreatitis, Centralbl. f. allg. Path. u. path. Anat. **16**: 903, 1905.
5. Zillner, E.: Ruptura flexurae sigmoidis inter partum, Virchows Arch. f. path. Anat. **96**: 307-318, 1884.
6. Boikan, W. S.: Meconium Peritonitis From Spontaneous Perforation of the Ileum in Utero, Arch. Path. **9**: 1164-1183, 1930.
7. Neuhauser, E. B. D.: Roentgen Diagnosis of Fetal Meconium Peritonitis, Am. J. Roentgenol. **51**: 421-425, 1944.
8. Litten: Cited by Rudnew.[2]

CLINICAL EXPERIENCES WITH THE ARTIFICIAL KIDNEY

CHARLES B. RIPSTEIN, M.D., JOHN T. MACLEAN, M.D.,
NANNIE K. M. DELEEUW, M.D., AND G. GAVIN MILLER, M.D., MONTREAL, CANADA

(From the Departments of Surgery and Urology, Royal Victoria Hospital and McGill University)

THE value of an artificial kidney in certain types of uremia was amply demonstrated during 1948. Following the pioneer work of Kolff[3] in Holland and Murray[5] in Canada, other papers have appeared reporting the successful use of such an apparatus.

The principle of utilizing dialysis to clear the blood of waste products was introduced by Abel, Rowntree, and Turner in 1913.[1] The application of this principle to the human patient was made possible by the clinical development of heparin as a safe, nontoxic anticoagulant. Various types of apparatus have been described, all of which are fundamentally similar. The machine used at the Royal Victoria Hospital is a Kolff artificial kidney with certain modifications. It consists essentially of a wooden drum around which 100 feet of cellophane tubing is wound in spiral fashion. This tubing has a flat diameter of one inch. The drum revolves at a constant speed of 25 revolutions per minute in a bath of the following composition:

NaCl	0.6%
KCl	0.04%
$NaHCO_3$	0.2%
Glucose	2.0%
Tap water	100 liters

The bath is kept at a constant temperature of 100° F.

In setting up the apparatus the patient is heparinized and a glass cannula is inserted into the radial artery and connected to the cellophane tubing. After passing through the machine the blood is returned into the antecubital vein by a variable speed pump.

The patient's blood is thus exteriorized across a semipermeable membrane, and the diffusible substances within the blood are brought into equilibrium with those in the bath water. By this means the excess nitrogenous waste products are removed from the circulation while the important electrolytes remain unchanged.

The chief value of such an apparatus is in the treatment of uremia due to reversible conditions of the kidney. A temporary clearing of the blood by dialysis may give the kidney time to recover from damage and resume function. In such cases the artificial kidney may be lifesaving. We have also found the machine useful in an occasional case with a permanent renal lesion. In many such patients there is sufficient kidney function to maintain life under ideal conditions. However, uremia may be precipitated by infection or other

Presented at the Forum on Fundamental Surgical Problems at the Clinical Congress of the American College of Surgeons, Los Angeles, Calif., Oct. 22, 1948.
Received for publication, Nov. 3, 1948.

complications, and the artificial kidney provides a means of helping such a patient over the crisis.

The types of uremia in which dialysis is of value can be summarized as follows:

1. Acute renal lesions with uremia
   (a) Fulminating acute glomerulonephritis
   (b) Acute poisoning—mercury, phenol, salicylates

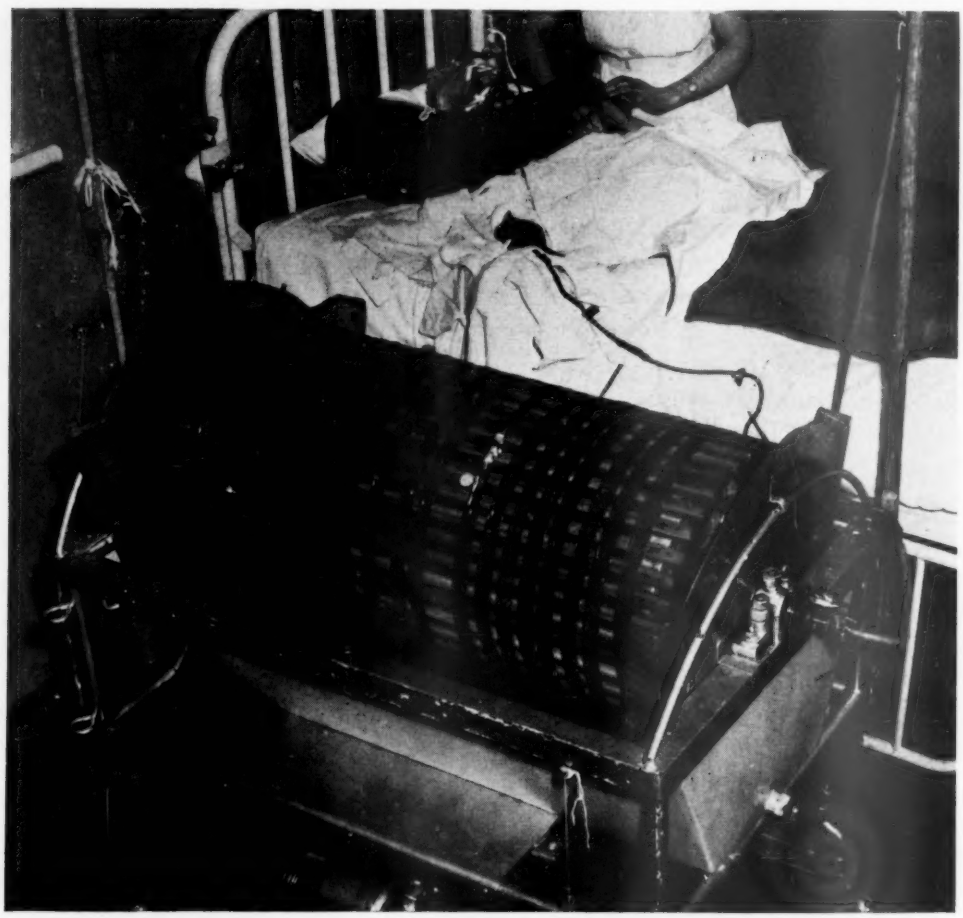


Fig. 1.—The artificial kidney in use.

2. Lower nephrone nephrosis type of lesion
   Anuria following (a) Incompatible transfusion
   (b) Sulfonamide administration
   (c) Crush syndrome
   (d) Severe burns
   (e) Eclampsia
3. Anuria following a prolonged period of hypotension
   Postoperative anuria
4. Preparation of the uremic patient for a surgical procedure

(a) Prostatic obstruction
(b) Infections of the kidney

In the past seven months we have treated six patients with uremia with the artificial kidney. The purpose of this paper is to outline the effects of this dialysis on the uremic state and on the patient as a whole.

Effect on Blood Chemistry.—It is obvious that the diffusible electrolytes in the blood will reach an equilibrium with those in the bath water. The cellophane tubing forms a semipermeable membrane which is impervious to larger molecules such as proteins.

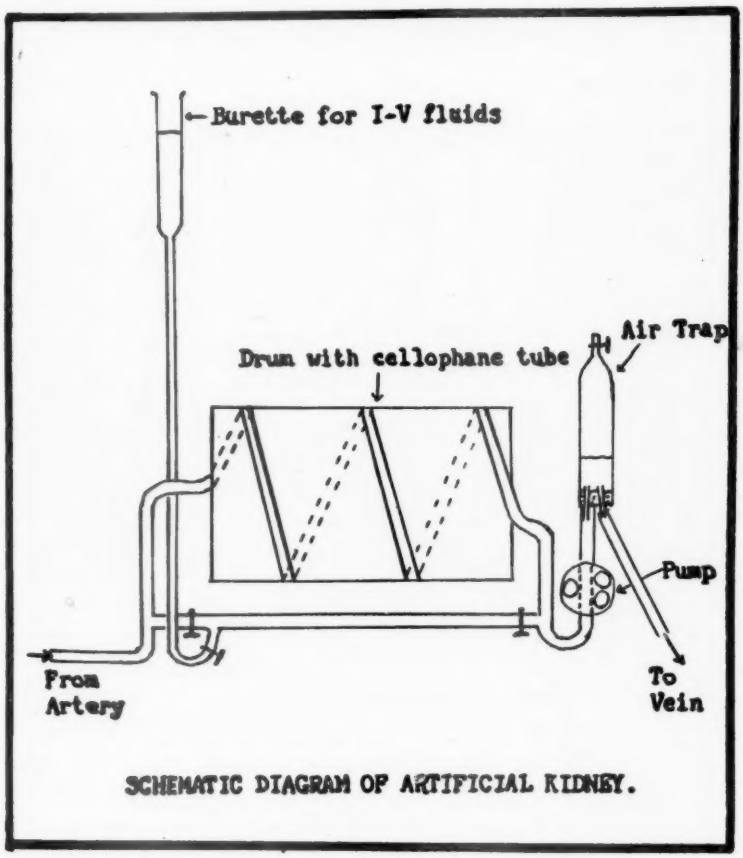


Fig. 2.—Diagram of the mechanism of the artificial kidney.

The nonprotein nitrogen of the blood drops at a rate of 10 to 30 mg. per cent per hour, while the bath water nonprotein nitrogen increases in proportion. The rate of diffusion slows as the dialysis progresses but we have never found it necessary to change the bath within an eight-hour period.

In many cases, the blood nonprotein nitrogen rises after the dialysis is stopped. This is because the excess nitrogenous wastes in the tissues are not discharged as quickly as they are removed from the blood by the kidney. This theoretically necessitates a longer period of dialysis, but in practice we have found that an eight-hour treatment is usually sufficient to clear the blood and improve the uremic condition.

The bath water is low in calcium because with an open tank and low CO_2 pressure, calcium salts tend to precipitate. The result is a gradual fall in blood calcium which can be prevented by giving the patient 10 Gm. of calcium gluconate intravenously every three hours.

If acidosis exists it may be aggravated by the dialysis. This tendency can be overcome by giving 500 c.c. of 1/6 molar sodium lactate intravenously whenever the CO_2 combining power falls below 50.

The bath contains a high concentration of glucose to prevent hemolysis. This diffuses into the blood and causes a hyperglycemia which may reach a level of 500 to 600 mg. per cent. It is important to avoid this effect in diabetic patients. In any case the administration of insulin may be advisable.

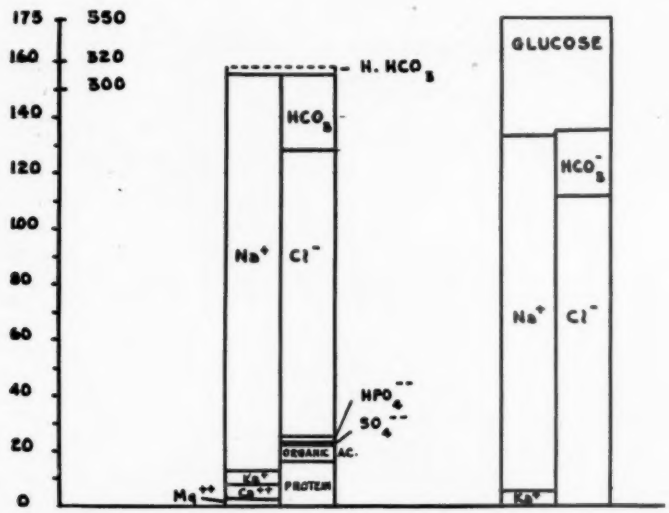


Fig. 3.—Comparison of the constituents of blood plasma to the dialyzing fluid.

Effect on Circulating Blood.—One of the early problems encountered in this work was the determination of the optimum dosage of heparin. It soon became apparent that heparin was lost by dialysis and large amounts were required to prevent coagulation. If the blood clots within the kidney the treatment must be abandoned, accordingly it is far better to use too much heparin than too little. An initial dose of 150 mg. is given to the patient intravenously and another 150 mg. is run through the kidney. Kolff has emphasized that metal connections must be avoided because they inactivate heparin. For this reason we have used glass cannulas and connections. During the course of the dialysis, 50 mg. of heparin is added to the circuit every 1½ hours. This routine has worked very well and we have had no trouble with clotting since its adoption. Blood heparin levels show an adequate concentration at all times. At the end of the treatment the heparin is neutralized by giving 10 c.c. of a 1 per cent solution of protamine sulfate intravenously.

The changes in the formed elements of the blood have been studied by DeLeeuw and Blaustein. They demonstrated a considerable degree of hemolysis in vitro which was due to the centrifugal effect of the drum and the mechanical action of the pump. In clinical cases this hemolytic effect does not appear to

be important. The white cells decrease in number at the beginning of the dialysis but return to normal within a few hours. This is due to coating of the cellophane with leucocytes because of a positive chemotaxis.

Effect on the Patient.—The process of dialysis with the artificial kidney is well tolerated even by the poor-risk patient. The machine does constitute an arteriovenous shunt, but the capacity of the shunt is only 200 c.c. a minute and this is not enough to embarrass the circulation. The rapid return of blood into the right side of the heart may theoretically cause a rise in venous pressure and lead to pulmonary congestion. So far we have observed no harmful effects. In all cases the pulse and blood pressure have remained constant throughout and there has been no evidence of cardiac failure.

No other significant effects of dialysis have been noted except for an occasional patient who has felt subjectively improved after a period of treatment.

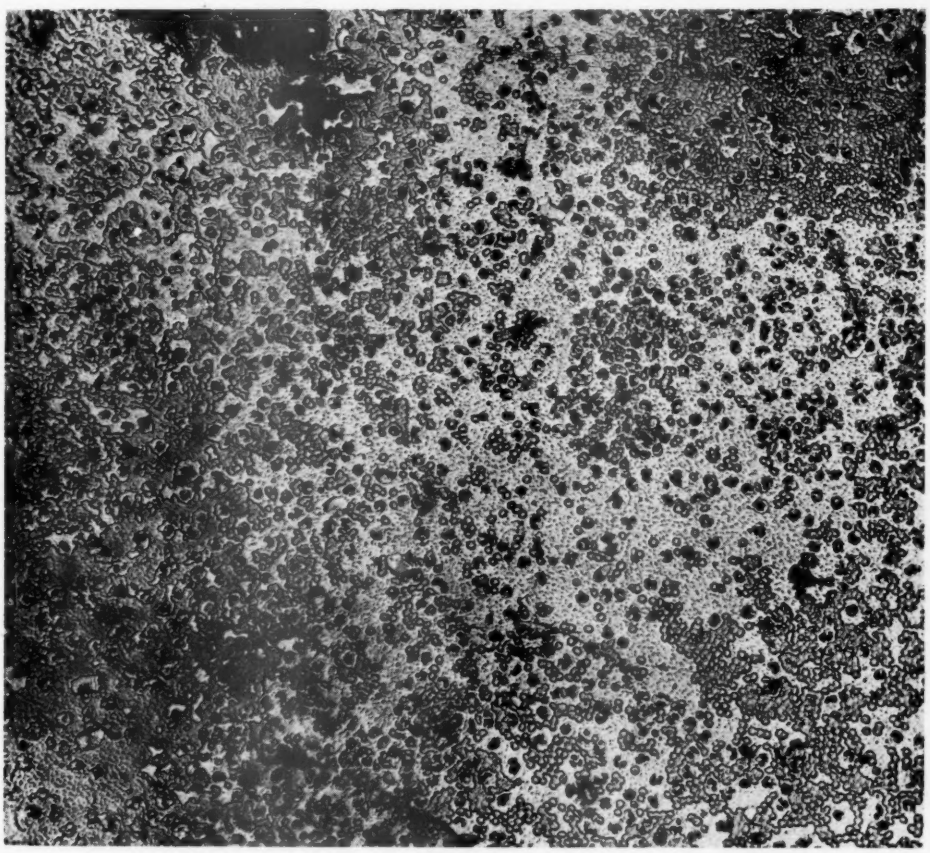


Fig. 4.—Section of the cellophane tubing showing trapped leucocytes.

CASE REPORTS

CASE 1.—A man, aged 69 years, had uremia due to prostatism complicated by cerebral arteriosclerosis and left lower lobe pneumonia.

Dialysis was carried out for three hours with a drop in the nonprotein nitrogen from 121.5 to 60.8 mg. per cent.

The patient was in moribund condition and died a few hours after treatment was discontinued. Autopsy showed marked degenerative changes in the kidneys.

CASE 2.—A man, aged 33 years, had anuria due to nembutal poisoning. Dialysis was carried out for one hour, during which time the nonprotein nitrogen dropped from 189 to 135.5 mg. per cent. Treatment was stopped because of clotting in the tubing. The patient continued to improve and the nonprotein nitrogen dropped to normal in forty-eight hours and the urinary output increased. The good result in this case can hardly be attributed to the artificial kidney.

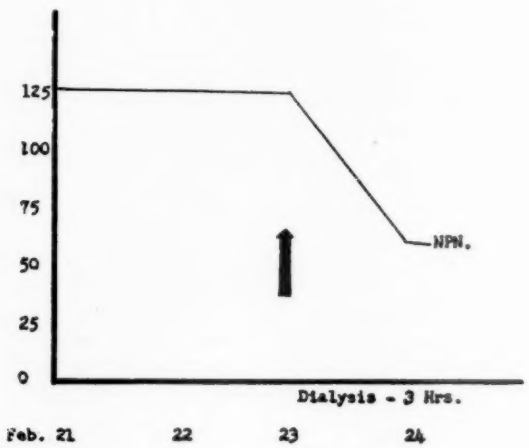


Fig. 5.—Chart of treatment in Case 1.

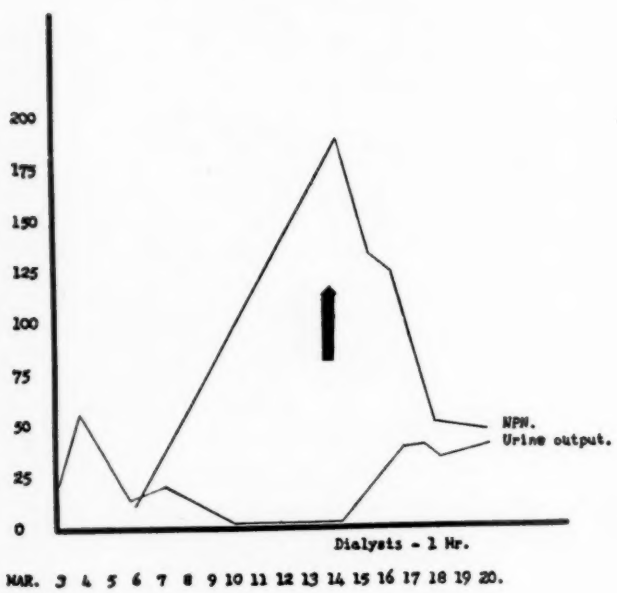


Fig. 6.—Chart of treatment in Case 2.

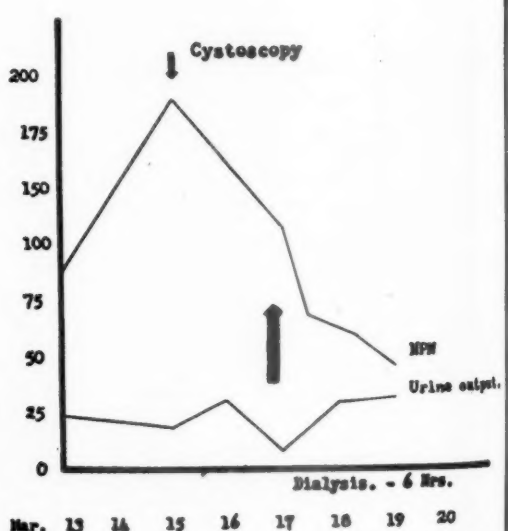


Fig. 7.—Chart of treatment in Case 3.

CASE 3.—A woman, aged 55 years, had anuria due to bilateral ureteral obstruction by secondary carcinoma. A six-hour dialysis caused a fall in nonprotein nitrogen from 102 to 48 mg. per cent with marked subjective improvement. She remained well for several weeks but the nonprotein nitrogen gradually rose and she died with uremia. Autopsy showed marked bilateral hydronephrosis and renal atrophy.

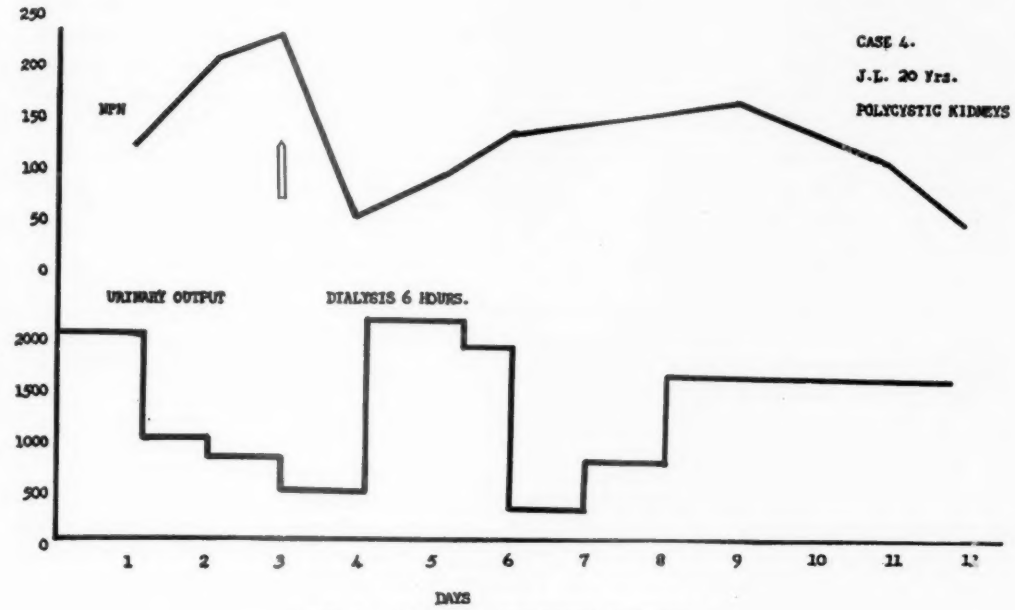


Fig. 8.—Chart of treatment in Case 4.

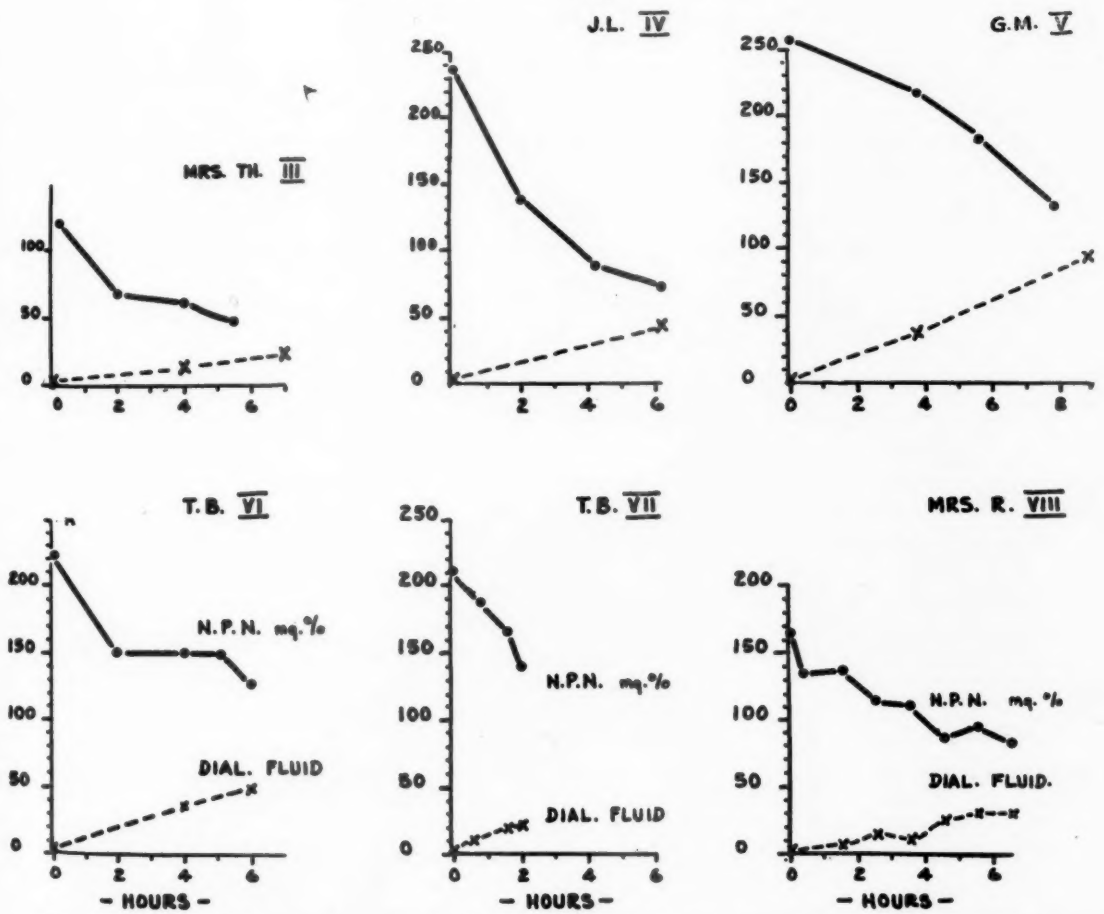


Fig. 9.—Charts of six patients treated with the artificial kidney, showing the fall in nonprotein nitrogen in the patient's blood and the corresponding rise in the bath water.

CASE 4.—A man, aged 20 years, had congenital polycystic kidneys with renal failure and uremia. His condition was moribund. Dialysis was carried out for six hours with a drop in the nonprotein nitrogen from 237 to 73 mg. per cent and creatinine from 15. to 4.3 mg. per cent. During the treatment 44.8 Gm. of nonprotein nitrogen were removed from the blood.

The following day the nonprotein nitrogen rose to 115 mg. per cent as further nitrogenous wastes were released from the tissues. After ten days the nonprotein nitrogen dropped to 60 mg. per cent and has remained at that level for the past four months. He is clinically well at present and is working. In this case the use of the kidney was a life-saving measure and despite a chronic renal lesion the patient has remained well for some time.

CASE 5.—A man, aged 27 years, had chronic glomerulonephritis with uremia. A nine-hour dialysis caused the nonprotein nitrogen to drop from 258 to 133 mg. per cent and the creatinine from 26 to 16.8 mg. per cent. (93.5 Gm. nonprotein nitrogen removed). The patient was improved after treatment and felt subjectively better for seventy-two hours. He then began to go downhill and died twelve days later. At autopsy the kidneys showed far-advanced disease.

CASE 6.—A man, aged 58 years, had postoperative anuria with renal failure. A six-hour dialysis caused the nonprotein nitrogen to drop from 224 to 128 mg. per cent (50 Gm. nonprotein nitrogen removed). Heparin level at the beginning of treatment was 40 gamma and during dialysis averaged 20 gamma. This indicates an adequate anticoagulant effect. The patient was subjectively improved the day following dialysis.

CONCLUSIONS

1. The artificial kidney is an efficient means of removing nitrogenous waste products from the blood in clinical cases of uremia.

2. Dialysis is well tolerated by the patient and does not produce any harmful effects.

REFERENCES

1. Abel, J. J., Rowntree, L. G., and Turner, R. B.: J. Pharmacol. & Exper. Therap. 5: 275, 1913.
2. Alwall, N.: Acta med. Scandinav. 127: 55, 1947.
3. Kolff, W. J.: New Ways of Treating Uraemia, London, J. & A. Churchill, Ltd.
4. MacLean, J. T., Ripstein, C. B., DeLeeuw, N. K. M., and Miller, G. G.: Canad. M. A. J. 58: 433, 1948.
5. Murray, G., Delorme, E., and Thomas, N.: Arch. Surg. 55: 505, 1947.
6. Murray, G., Delorme, E., and Thomas, N.: J. A. M. A. 137: 1586, 1948.

Case Reports

GIANT PHARYNGOESOPHAGEAL DIVERTICULUM

Case Report

Robert A. Mino, M.D., and Arthur I. Murphy, Jr., M.D., Wilmington, Del., and Robert G. Livingstone, M.D., Cambridge, Mass.

(From the Surgical Service of Memorial Hospital, Wilmington, Del.)

FREQUENT reference has been made in recent literature to the problems met with in the treatment of pharyngoesophageal diverticula. Lahey (1940, 1946), Harrington (1945), and Shallow (1948) have discussed the subject thoroughly in the presentations of their respective groups of cases, while McNealy (1947), King (1947), and Sweet (1947) in their reports have also given information of great value in the management of these lesions. The present communication affords a review of our experience with a pharyngoesophageal diverticulum, apparently of unequaled size.

CASE REPORT

H. J. (Hosp. No. 75,240), a Negro butler 52 years old, was admitted to the Medical Service of the Memorial Hospital on Sept. 10, 1947, because of weakness and dysphagia of about six months' duration.

The symptoms had begun with the regurgitation of a portion of each meal. Liquids were retained at first, provided they were taken slowly, though with each attempt to swallow, gurgling sounds were usually heard and associated with a transient sensation of pressure in the chest. No medical attention was requested until weakness was experienced approximately five months later. A physician then discovered that the patient at that time weighed 130 pounds. A fluoroscopic examination was performed, and immediate hospitalization was advised. This proposal frightened the patient, and he refused all further attention. Five weeks later swallowed liquids could no longer be retained, and shortly afterward referral to the hospital was reconsidered and accepted.

Physical Examination.—At admission he was found to be a strikingly enfeebled and emaciated patient who looked desperately ill. Temperature was 98.6° F., pulse 80, respiratory rate 20, blood pressure 116/84, weight 94 pounds. Numerous hard, nontender lymph nodes were palpable on each side of the neck. The trachea was in the midline, and the thyroid gland was not abnormal. On the right the area of mediastinal dullness was extended to the midclavicular line, and over it the breath sounds were considerably diminished. The other findings which were noted were not thought to be abnormal.

Laboratory Studies.—The hemoglobin concentration was 13.5 Gm. The red and white cell counts were 4,150,000 and 22,300, with a differential white count of 82 per cent neutrophils, 14 per cent lymphocytes, and 4 per cent monocytes. Blood urea nitrogen 52 mg. per cent, plasma chlorides 428 mg. per cent, plasma proteins 7.9 Gm. per cent. The urine was not found to be abnormal.

Roentgenograms revealed an enlarged oval mass lying in the mediastinum and in the right upper chest (Figs. 1 and 2). Its superior and inferior poles were opposite the first and sixth thoracic vertebrae, respectively. The lateral border of the mass was about 9 cm. from the midline of the chest, encroaching on the pleural cavity and compressing the right lung, while anteroposteriorly the mass was almost centrally located, with a maximum diameter of about 9 cm. A definite fluid level was apparent in its cavity. The lower margin of the

Received for publication, Oct. 30, 1948.

Fig. 1. Fig. 2.

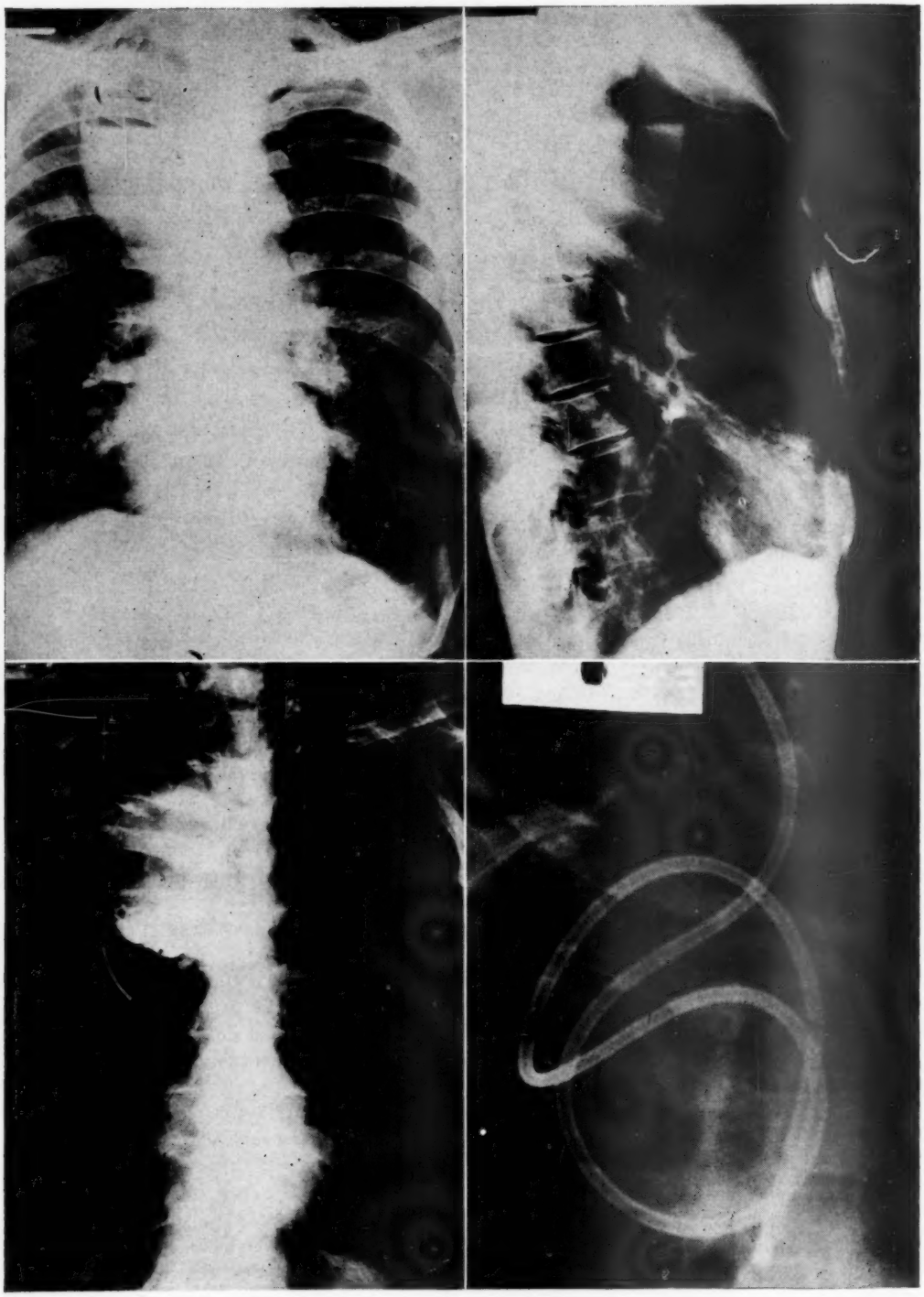


Fig. 3. Fig. 4.

Figs. 1 and 2.—Roentgenographic appearance of the diverticulum on admission. The fluid level is apparent in the anteroposterior view.

Fig. 3.—Demonstration of the lower margin of the diverticulum after a barium mixture had been swallowed. None of the barium has passed into the distal part of the esophagus.

Fig. 4.—Further roentgenographic demonstration of the size of the diverticulum, obtained during an attempt to pass a Levine tube into the stomach.

mass was demonstrated when a small amount of a diluted barium mixture had been swallowed (Fig. 3). With complete filling of the cavity no barium was seen to pass into the distal part of the esophagus, and during forceful exhalations with the epiglottis closed no change was observed in the size or in the outline of the mass. It was also later noted that the mass did not collapse when its cavity had been carefully emptied by lavage.

Scars were also noticed in the apex of each lung, and discrete calcified nodules were reported in the perihilar areas and in the peripheral fields. These findings were regarded as evidence of healed tuberculosis.

Preoperative Treatment.—A regimen of parenteral feedings was immediately begun, but within five days a weight loss of ten pounds had been recorded. Numerous attempts were made to pass a Levine tube into the stomach (Fig. 4). When these efforts were abandoned a surgical consultation was requested. An emergency jejunostomy was performed, and within three weeks a weight gain of twenty-six pounds was achieved. A microcytic anemia which was discovered when the dehydration had been corrected responded to transfusions with three pints of fresh whole blood.

A cervical lymph node was excised and found to be tuberculous.

One month after hospitalization an esophagoscopy was performed. The diverticulum was entered directly, and its lower margin was encountered 28 cm. from the upper incisors. The orifice of the distal part of the esophagus was not seen. The diverticular walls were thought to be fibrotic and adherent to the surrounding tissues. There was no evidence of active inflammation or of neoplastic change.

Operative Treatment.—A two-stage operation of the type described by Lahey was therefore undertaken (by R. A. M.) in the treatment of this lesion. Satisfactory anesthesia was obtained with the administration of nitrous oxide, oxygen, and ether through an intratracheal tube.

The first stage of the procedure was performed on Oct. 13, 1947, after the diverticulum had been emptied by lavage. An incision at the anterior edge of the right sternocleidomastoid muscle was extended from the sternum to the level of the hyoid bone and carried through the skin, platysma, and deep fascial layers. The anterior belly of the omohyoid muscle was transected near the point of its attachment to the hyoid bone. The right superior, middle, and inferior thyroid veins were ligated and divided. Access to the diverticulum was provided through the space between the structures of the right carotid sheath and the right lobe of the thyroid gland. The pretracheal fascia was incised, and the right inferior thyroid artery was ligated and divided.

The mobilization of the diverticulum was very difficult because of the fibrotic, extensive adhesions about its walls. Gentle traction with sponge forceps was found to be of no assistance in the development of a cleavage plane, but eventually recourse to intermittent air injections through the lavaging tube was discovered to be helpful in this phase of the dissection. When the diverticulum had finally been delivered from its bed its point of origin was palpable as a rounded orifice 4 cm. in diameter which lay posteriorly in the midline and immediately below the inferior pharyngeal constrictor muscle.

The size of the remaining mediastinal defect could not be diminished by inflation of the lungs. The cavity was therefore packed with gauze which was inserted about a rubber catheter. The dissection was resumed until the submucosa of the neck had been exposed. The tip of the lavage tube was then guided into the distal part of the esophagus. The diverticulum was implanted in the wound in a position which assured an obtuse angle at the junction of its neck with the esophagus. There was no resultant traction on the wall of this structure. Multiple purse-string sutures were taken in the walls of the fundus of the diverticulum to reduce its bulk. The skin incision was then closed about the free end of the catheter. This entire operation was tolerated well, and the patient was returned in excellent condition to his bed.

The postoperative course was uneventful. Ambulation was encouraged after full recovery from the anesthesia. The jejunostomy feedings were continued. The lavage tube was withdrawn on the second day, and liquids were thereafter administered by mouth. A penicillin solution was injected into the catheter each day. The mediastinal pack was removed in seven days.

The second stage of the procedure was performed on Oct. 23, 1947. The various structures in the wound had not been altered in appearance. Traction sutures were inserted in the walls of the hypopharynx and esophagus near the diverticular orifice. Mosquito clamps were placed upon the diverticular neck along the proposed line of amputation, and the tissues medial to the clamps were then divided. Immediate closure of the sectioned layers was made with interrupted mattress sutures of fine chromic catgut. This sequence of clamping, incision, and repair was continued until the diverticulum was excised and the esophageal orifice was closed in its longitudinal diameter. The suture line was re-enforced with interrupted mattress sutures of fine chromic catgut placed in the muscle layers of the esophagus and hypopharynx. The residual mediastinal defect was packed with gauze. The patient tolerated the operation well.

Fig. 5.—Roentgenographic appearance of the esophagus nine months after operation. There are no abnormalities of the pharynx or esophagus.

Early ambulation was again encouraged, and the regimen of jejunostomy feedings was continued. The lavage tube was removed on the third postoperative day. The pack was gradually withdrawn from the mediastinal defect and finally discarded early in the second week. To expedite the closure of the small remaining defect the patient was instructed to make forceful exhalations with the epiglottis closed at frequent intervals each day. Within two weeks the defect was believed to have been closed, but a low-grade fever, discovered somewhat later, was then thought to be indicative of a walled-off abscess in this site. The sinus tract was therefore opened, and a small amount of seropurulent liquid was disclosed. The temperature was normal the next day. Oral feeding was begun, and on the thirty-third postoperative day the jejunostomy tube was taken out. Shortly afterward the patient was discharged, able to enjoy an unrestricted diet and retain it normally.

The mediastinal defect was found to be filled in approximately three weeks later. Roentgenograms at four and nine months after operation showed no abnormalities of the pharynx, hypopharynx, or esophagus (Fig. 5). A steady weight gain has been noted since the time of operation, and at the most recent visit, Sept. 2, 1948, a weight of 157 pounds was recorded.

Microscopic Examination.—The specimen was lined with epithelium of the type which is normally encountered in the esophagus. The walls were found to be fibrotic and infiltrated with many groups of plasma cells. There was no evidence of malignant change. Diagnosis was pharyngoesophageal diverticulum.

COMMENT

Though pharyngoesophageal diverticula are not infrequently encountered, those of the proportions here described are apparently extremely rare. We have found no previous record of a larger diverticulum of this type, and we know of no reported instance where compression of the lung was a coexistent finding.

We believe that certain aspects of the treatment of the larger diverticula merit special emphasis. A preliminary jejunostomy may be a lifesaving procedure when dysphagia has led to marked nutritional deficiency. The value of this measure in the case reported here, where a gain of twenty-six pounds was recorded in a period of three weeks, has seemed indisputable to us. Another point of great importance is the technique of dissection once a decision to excise the diverticulum has been made. An adequate exposure is a prime essential, and in our opinion a generous incision of the type we have described provides the only surgical approach which will suffice in this respect. Unusual care is required also in division of the adhesions between the diverticulum and the walls of the esophagus. A technique of intermittent air injection, as applied to these lesions, may be of value in the development of a satisfactory cleavage plane and thus in the avoidance of inadvertent injury to other mediastinal structures.

Our preference for the two-stage operation in the treatment of a diverticulum of this size will not be debated here. The many fascial planes invaded in the course of the dissection undoubtedly increase the risk of complicating cellulitis or infection of the mediastinum. We believe that we were able to minimize these dangers in this case by waiting for the sealing of the opened planes before we finally completed the removal of the diverticulum.

SUMMARY

The occurrence of a giant pharyngoesophageal diverticulum is reported, and an account is given of its successful surgical removal.

A technique of intermittent air injection is also suggested as a means of aiding in the dissection of the sac, and use of the two-stage operation is unreservedly endorsed in the operative treatment of the larger diverticula of this type.

REFERENCES

1. Harrington, S. W.: Pulsion Diverticulum of the Hypopharynx at the Pharyngoesophageal Junction, SURGERY **18**: 66-81, 1945.
2. King, B. T.: New Concepts of the Etiology and Treatment of Diverticula of the Esophagus, Surg., Gynec. & Obst. **85**: 93-97, 1947.
3. Lahey, F. H.: Esophageal Diverticula, Arch. Surg. **41**: 1118-1140, 1940.
4. Lahey, F. H.: Pharyngo-esophageal Diverticulum: Its Management and Complications, Ann. Surg. **124**: 617-636, 1946.
5. McNealy, R. W., and Glassman, J. A.: A One-stage Pharyngoesophageal Diverticulectomy, SURGERY **21**: 470-475, 1947.
6. Shallow, T. A., and Clerf, L. H.: One Stage Diverticulectomy: Improved Technique and Analysis of 186 Cases, Surg., Gynec. & Obst. **86**: 317-322, 1948.
7. Sweet, R. H.: Pulsion Diverticulum of the Pharyngoesophageal Junction: Technique of the One-stage Operation, Ann. Surg. **125**: 41-48, 1947.

PNEUMONECTOMY FOR PULMONARY TUBERCULOSIS IN A WOMAN SIX MONTHS PREGNANT, FOLLOWED BY A NORMAL BIRTH

SAMUEL ALCOTT THOMPSON, M.D., AND SYDNEY BRESSLER, M.D.
NEW YORK, N. Y.

PNEUMONECTOMY for unilateral caseous-pneumonic tuberculosis which cannot be controlled by collapse measures has become an accepted procedure. In the treatment of tuberculosis complicated by pregnancy, all cases are individualized, although certain general standards are followed at the Metropolitan Hospital. If the caseous-pneumonic disease is discovered after the first trimester of pregnancy, it is the policy not to be concerned with the pregnancy, but rather to use any measure which would control the disease in the mother. Thus, all types of collapse therapy have been used in the past. We have now another procedure, which, when the proper indications exist, can be added to the list, namely, pneumonectomy. This case is being reported because it illustrates the trend in the treatment of tuberculosis complicated by pregnancy, and also because no similar case can be found reported in the recent literature.

Patient A. C., a 29-year-old Puerto Rican woman, was admitted to the Tuberculosis Service on Oct. 16, 1947, with the diagnosis of pulmonary tuberculosis. She was well until one month prior to hospitalization, when she noted the onset of a cough, productive of greenish-yellow sputum without blood, weakness, afternoon fever, and night sweats. She was pregnant at this time and a chest x-ray film revealed the pulmonary disease.

Physical examination revealed a well-developed, poorly nourished, Puerto Rican woman looking chronically ill but in no acute distress. There was increased tactile fremitus and dullness over the left side of the chest. Post-tussic râles were heard over the left apex. The heart showed no enlargement, murmurs, or arrythmias. Abdominal examination revealed a gravid uterus.

The following menstrual history was obtained: Onset at 16 years of age. The periods were always regular, 28-day cycle, with a flow for three days. Her first child was born on Feb. 27, 1947. Menstruation began again in April, 1947. She had normal periods in May and June. The period in July was abnormal so that it only lasted for two days and the flow was spotty. This was the last menstrual bleeding.

A chest x-ray film on Oct. 17, 1947, revealed the right lung to be clear. The trachea, heart, and mediastinum were shifted to the left. The left lung showed a marked pleural thickening and homogeneous clouding throughout. In the left infraclavicular area numerous highlights suggesting cavitation were noted. The sputum was positive for tubercle bacilli on direct smear, Gaffky 2. A diagnosis of extensive caseous-pneumonic disease, with cavitation of the left lung was made.

Control of the disease by artificial pneumothorax was attempted. A left pneumothorax was successfully induced on Oct. 21, 1947. After two weeks, it was noted that the pneumothorax had failed to influence the cavities. A further study showed the lung to be adherent to the posterior chest wall over a wide area in the region of the cavities.

At a surgical tuberculosis conference on Nov. 26, 1947, it was the consensus of opinion that the interruption of a five- to six-month pregnancy would be a hazardous procedure, and to allow the patient to go on with the pregnancy with an uncontrolled disease would be inviting disaster. It was therefore decided to treat the tuberculosis and allow the pregnancy to continue. A pneumonectomy was advised. The preoperative pulse rate ranged between 100 and 110. The blood pressure was 130/80. Ventilatory tests showed that pulmonary

Received for publication, Sept. 24, 1948.

function was adequate for pneumonectomy. Bronchoscopy and electrocardiograms were normal. The hemoglobin was 10.2 Gm. per cent. Fetal heart sounds and fetal movements were present. Three days prior to operation the patient was placed on 25 mg. of stilbestrol three times daily and 10 mg. of progesterone twice daily. She received transfusions of 500 c.c. of citrated blood daily for two days preceding the operation.

A left pneumonectomy was performed on Dec. 8, 1947, under cyclopropane endotracheal anesthesia. The patient was placed in the prone position with the left side of the body at the edge of the table. A posterolateral incision was made and the pleural space was entered through the sixth interspace. The mediastinal pleura was incised exposing the bronchus, which was cleared and divided between clamps. The pulmonary artery, superior pulmonary vein, and inferior pulmonary vein, in the order named, were individually cleared, doubly ligated, and transfixed and divided. The lung was then delivered by separating a few adhesions to the mediastinal pleura. The bronchial stump was then closed by a proximal row of mattress silk sutures. The cuff of bronchial tissue in the clamp was excised and a distal row of end-over-end silk sutures completely closed the bronchus. The bronchial stump retracted from sight into the mediastinum. The diaphragm was paralyzed by resecting a segment of the phrenic nerve. The wound was closed in layers, without drainage. At the completion of the operation, the intrapleural pressure was reduced –12 to –6.

The patient's condition was good during the operative procedure which lasted three hours and twenty minutes. She received 1,350 c.c. of blood and 1,300 c.c. of other fluid during the operation.

The postoperative course was excellent. Fetal heart sounds and movements were constantly present. The mediastinum was maintained in as neutral a position as possible by repeated thoracenteses. Penicillin, 50,000 units every three hours, which had been started three days before operation, was continued for two weeks. Streptomycin was not administered because of its possible danger to the fetus. The stilbestrol and progesterone were continued for sixteen days postoperatively.

The pathologic report was as follows. Gross: The specimen consisted of a left lung. The lobes were distinct. The external surface was dull red in color and shaggy. There was decreased crepitus throughout. At the apex of the upper and of the lower lobe were palpable nodular masses. On section these nodules were found to be caseous and necrotic masses surrounded by miliary caseous areas. Microscopic: Lung tissue had an exudative appearance in the alveoli and many areas of caseation surrounded by epitheloid cells and many multinucleated giant cells.

After the immediate postoperative period (first two weeks) the course was uneventful except for the maintained rapid pulse, 100/110. Fetal movements were present and quite active. The urine consistently showed 1 to 2 plus albumin. Frequent blood pressure readings were normal. There was no evidence of toxemia of pregnancy. The sputum was converted to negative immediately after the operation and has remained so.

On Feb. 5, 1948, the patient was again presented to the combined medical-surgical conference, and here it was the consensus of opinion that inasmuch as it was not known how a patient would fare with a labor following pneumonectomy, delivery by cesarean section would be the procedure of choice. However, at 8 A.M. on Feb. 18, 1948, a premature labor started with rupturing of the membranes. The patient was transferred to the obstetrical division. The obstetrical consultants at this time were of the opinion that inasmuch as the baby was small, delivery from below could be accomplished safely and easily. The second stage of labor started at 4 P.M. of this day, and one-half hour later, with the aid of outlet forceps, a normal male infant weighing 5 pounds, 1 ounce, was delivered. The mother showed no untoward effects.

The day following the delivery, the pulse rate was 88, the first time that it had been below 100 since her transfer to the thoracic surgical service. Her post-partum course was uneventful and after three weeks she was returned to the tuberculosis service for further convalescence. Fourteen months after the operation both mother and child were in excellent condition and the mother's sputum was still negative for acid-fast bacilli.

CALCULOSIS AND FIBROSIS OF THE PANCREAS

JOHN H. BOGLE, M.D., BROOKLYN, N. Y.

(From the Department of Surgery, The Brooklyn Hospital)

THE syndrome of pancreatic calculosis and fibrosis associated with intractable abdominal pain is apparently being recognized with increasing frequency. Over 200 cases of pancreatic lithiasis have been reported in the literature. The impetus that the work of Whipple and others has given to surgery of the pancreas and duodenum, along with improvements in anesthesia and modern supportive treatment, has encouraged surgeons to attempt more frequent radical surgical attacks on the pancreas. A good summary of the subject, with a bibliography, is contained in a recent article by Eliason and Welty.[1]

The object of this paper is to discuss briefly the surgical treatment of pancreatic calculosis and fibrosis and to report a case successfully treated by subtotal resection of the pancreas.

Undoubtedly many cases of pancreatic lithiasis occur without symptoms and it is seen occasionally as an incidental finding on a roentgenogram of the abdomen. Stones in the pancreas that are causing symptoms may be obscured, however, by the barium in a gastrointestinal series, so that a plain film should always be made.

The following methods of treatment have been recommended and used with reported success:

1. Pancreolithotomy
2. Pancreatic resection
3. Total pancreatectomy
4. Ligation of the pancreatic ducts
5. Sympathectomy and vagotomy

Pancreolithotomy.—The most frequently used procedure has been pancreolithotomy. If there are only a few large calculi present in a localized area of the pancreas, incision into the pancreas and ducts with removal of the stones would seem a logical procedure. However, calculi can be and have been missed and left behind. A roentgenogram taken through the wound at the time of operation might be helpful in determining this point. It should also be remembered that the gland is a damaged one, with fibrosis, loss of parenchymal tissue, and dilatation of ducts with ulceration and derangement of the ductal epithelium.

The fibrosis may play as large or a larger part in producing pain as did the stones. And finally the cause or causes that initiated the pathologic process may still be operating and the stones may re-form, fibrosis may proceed, and pain continue.

Read at a meeting of the Brooklyn Surgical Society, May 6, 1948.
Received for publication, Oct. 25, 1948.

Pancreatic Resection.—The resection of the involved part of the pancreas, by removing the presumed source of the pain, would seem to promise a cure. The head is the most frequently involved part of the gland and to remove it the duodenum must be excised also. With involvement of the entire gland, resection of all of it except a strip in the curve of the duodenum allows the duodenum to be undisturbed, leaves some glandular tissue for internal and external secretion, and would offer a reasonable prospect for the relief of pain. This was the procedure adopted in the case being reported.

Total Pancreatectomy.—The complete removal of the source of the patient's pain is logical and has been successful in the hands of Whipple[2] and others. It is a radical procedure and a formidable one, involving, besides the removal of the pancreas and the duodenum, resection of the stomach and common bile duct and implantation of the duct into the jejunum, with a gastroenterostomy. The patient is made diabetic, and the operation must certainly carry a higher risk than the less radical procedures.

Ligation of the Pancreatic Ducts.—The theoretical basis for the ligation of the pancreatic ducts is that if the excretory duct of a gland is ligated the secreting parenchyma will atrophy, swelling and distenton will disappear, and the gland will be converted to painless fibrotic tissue. The difficulty here lies in the fact that the stones have already blocked the ducts and the pancreas has been largely converted to fibrous tissue—the factors which seem to cause pain in this syndrome. The discrepancy perhaps may be due to incomplete blockage of the ducts by stones so that secretion is not completely suppressed. A successful case has been reported.[3] However, in that instance the ducts were not isolated and ligated but several mass sutures were apparently passed through the head of the pancreas and tied, the assumption being that the ducts were occluded by this maneuver. This would seem to be a rather unsatisfactory procedure. The isolation of the pancreatic ducts as they enter the duodenum in the living patient is difficult and somewhat hazardous. I believe there is little reason to recommend this operation at present.

Sympathectomy and Vagotomy.—The predominant disabling feature of this disease is pain, for which the patient seeks relief, and the various procedures outlined are directed toward that end. The cure of an extensively damaged pancreas is impossible in most cases. Regardless of the method of treatment employed, we are treating the pain rather than the disease. By interrupting the pain-carrying pathways from the pancreas, relief should be obtained. It is a rational procedure and has been reported as being successful.[4, 5]

The following case is being reported because it has certain features of interest. The patient was young, 26 years, with extensive calculosis and fibrosis of the pancreas, without diabetes. Bilateral sympathectomy and vagotomy, the latter both subdiaphragmatic and supradiaphragmatic, had been performed, without permanent relief of pain. A subtotal resection of the pancreas gave relief from pain without causing diabetes or digestive disturbances.

CASE REPORT

C. J., a white man who worked as a stock clerk, 26 years of age, was admitted to The Brooklyn Hospital on March 5, 1948. The chief complaints upon admission were severe abdominal pain, nausea, and vomiting for several days.

The past history was interesting. He had been in good general health until five years before, when he had had an attack of severe epigastric pain, nausea, vomiting, and weakness. He consulted a physician, who prescribed an ulcer diet which he followed irregularly.

He was married about that time and the history of the marriage becomes intermingled with that of the illness. Intermittent attacks of abdominal pain recurred over the next three years. During this period marital difficulties developed and he began to drink. Whatever the origin of the drinking may have been, as the attacks of pain became more severe, he drank more and more to relieve the pain. At times the pain was so severe that either twenty-five glasses of beer or a quart of whisky was the only thing that gave relief. The pain was described as of severe, agonizing, boring quality, extending through to the back and around the sides of the chest, and leaving him weak and nauseated. It did not seem to be related to any type of food or to the time food was taken.

In 1946 the patient entered a hospital in New York. There, a diagnosis of duodenal ulcer and "pancreatic stones" was made by roentgenogram. A right-sided thoracolumbar sympathectomy was performed. The patient left the hospital without having the left side operated upon for some reason, but he experienced some relief of pain for several months. However, the pain recurred, the attacks became more frequent, and during a severe attack he entered a hospital in Brooklyn about nine months before the present admission. While there, the abdomen was explored and the pancreas was found to be greatly enlarged, edematous, and hyperemic. A diagnosis of acute pancreatitis was made and an infradiaphragmatic vagotomy was performed. After this operation the pain was relieved for several months. Again the pain reappeared and became worse, and about five months after the second operation the patient was admitted to another hospital in Brooklyn. There, a left-sided transthoracic sympathectomy and supradiaphragmatic vagotomy were performed. After this operation he was relieved of pain for about two months.

Seven days before the patient's admission to The Brooklyn Hospital he again began to have severe upper abdominal pain, going through to the back. This was intermittent and at times agonizing in severity. Nausea and vomiting had occurred daily and he could retain only fluids. Four days before admission he passed several tarry stools but the stool was of normal color the following day. Appetite was very poor. There had been considerable loss of weight in the past few years, from 160 to 138 pounds. He had recently noticed that the bowel movements had become more frequent, four to five a day, and the stools were very loose.

Past history revealed that as a child the patient had been very close to his mother and feared and disliked his father. When he was 10 years old his mother died of heart disease and from that time until the age of 13, he suffered frequent epileptic seizures.

Physical examination upon admission revealed a 26-year-old man in acute distress, vomiting and complaining of upper abdominal pain. Color was good. The examination was negative except for the abdomen. It was soft and not distended. Tenderness without muscular spasm was present in the epigastrium and the left lower quadrant. No masses could be felt. Right thoracolumbar, left thoracotomy, and left upper rectus abdominal scars were present. Tenderness was present over the vertebral spines from the twelfth thoracic to the first lumbar.

A plain roentgenogram of the abdomen demonstrated a considerable number of irregular calcific densities extending throughout the head, body, and tail of the pancreas.

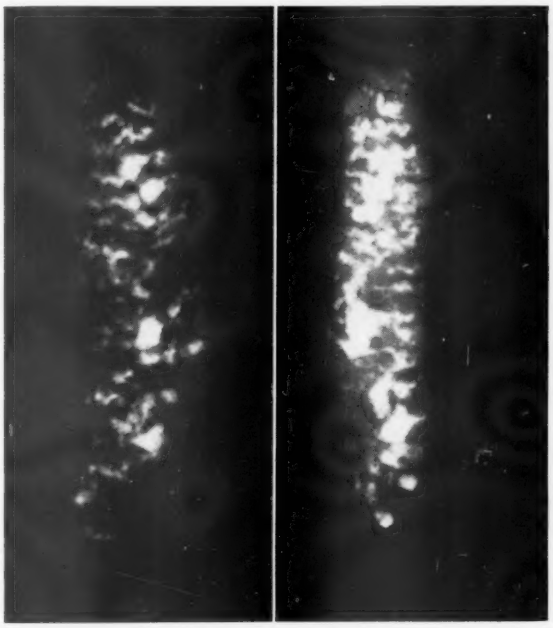
Laboratory work-up showed a normal urinalysis and blood count. The Wassermann reaction was negative. The blood urea, the creatinin, the serum amylase, and lipase were within normal limits. Fasting blood sugar was 85 mg. per 100 c.c. Blood cholesterol was 108 mg. per 100 c.c.

The insulin test revealed free hydrochloric acid in the gastric secretion, ranging from 2 to 18 clinical units. This would seem to indicate that despite two vagotomies, vagal fibers to the stomach were still present. A glucose-tolerance test gave successive values of 80, 125, 105, and 82 mg. per 100 c.c. for blood sugar.

Gastrointestinal roentgenograms showed a stomach that emptied slowly with some retention of barium after five hours, and a large atonic duodenal bulb associated with a zone of narrowing in the mid-portion of the second part of the duodenum at the level of the calcareous densities in the head of the pancreas. Some deformity of the first portion of the duodenum was present but there was no evidence of an active ulcer.

The patient was observed in the hospital for the next nineteen days. During this period he continued to complain of abdominal pain, very severe at times, with vomiting.

It soon became apparent that the patient had a psychopathic personality. He was unreliable and at times surly and unpleasant to the nurses and other patients on the ward. As his history had indicated, the psychic background had been poor since childhood. He was examined by neurologic and psychiatric consultants and found to have no organic nervous disease but to have some psychopathic traits with inadequacy and to be a dependent type emotionally, requiring an "emotional crutch."



A. *B.*

Fig. 1, *A* and *B*.—Roentgenogram of the pancreas after excision.

It was felt that the patient needed psychiatric treatment. He had had three operations with transient relief from pain but the pain had always recurred. We were therefore reluctant to advise further surgery for fear that a large part of the symptoms was psychogenic, and it would merely result in leaving him with another scar as well as the pain. Accordingly, a program of psychotherapy was outlined for him and plans were made to have him treated in a psychiatric clinic. He then flatly refused to follow this advice and begged for surgery to relieve the pain. Since obvious organic disease was present which could be the cause of the symptoms, it was decided to try to break the possible vicious cycle by resecting the pancreas.

On March 24, 1948, he was operated upon. Anesthesia was induced with sodium pentothal, followed by intratracheal cyclopropane, oxygen, and helium, with intravenous curare. The abdomen was opened through a transverse upper abdominal incision, cutting across both rectus muscles.

A moderate number of adhesions were encountered, which were separated, and the pancreas was approached through the gastrocolic omentum. It was found to be of about normal size, extremely fibrotic, and densely adherent to the surrounding tissue. The gall bladder was thin walled, contained no stones, and emptied easily. No ulcer was palpated in the duodenum. Mobilization of the gland was begun by freeing the tail from the surrounding tissue and proceeding from the left to the right. Considerable force was required to insert a needle carrying a traction suture into the gland. Extremely dense fibrous tissue surrounded the gland, necessitating sharp dissection, and it was necessary to clamp and ligate innumerable bleeding vessels, including the splenic artery. The spleen was buried in adhesions and was not removed.

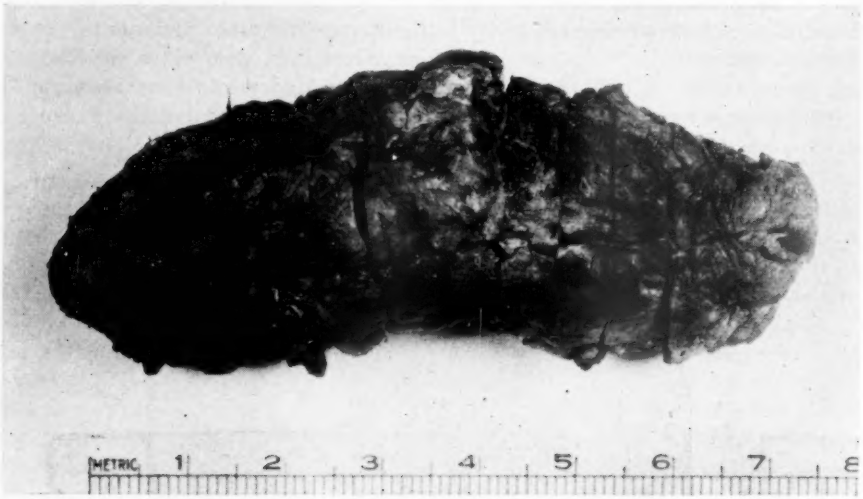


Fig. 2.—Photograph of the gross specimen. On the right can be seen a dilated duct where the head of the pancreas had been coned out and cut across.

Fig. 3.—Transverse section of the pancreas. The fibrotic character of the gland can be seen, as well as a dilated duct containing stones.

The pancreas was resected by coning it out at the head, to the right of the superior mesenteric vessels. Thus part of the head remained, between the duodenum and the superior mesenteric vessels which were entirely uncovered when the pancreas was removed. It is believed that 85 to 90 per cent of the pancreas was excised.

The cut end of the pancreas was closed over with cotton sutures and peritonized fat sutured over it. A large fenestrated tube was inserted to the pancreatic bed and brought out through the center of the wound. A catheter for suction drainage was placed in the large tube. The wound was closed with cotton and wire sutures.

The operating time was five hours and fifty minutes. Whole blood, totaling 1,500 c.c., was given during the operation. The blood pressure during the procedure stayed at about 120 systolic and 60 diastolic. The pulse ranged between 80 and 100, and respirations 18 to 25 per minute.

Postoperatively the patient did exceptionally well. Temperature rose to 100.5° F. the day of the operation and after that remained normal. There was practically no drainage through the catheter in the drainage tube which was kept under constant suction, and the tube was removed in forty-eight hours. He was out of bed on the third day. Fluids by

Fig. 4.

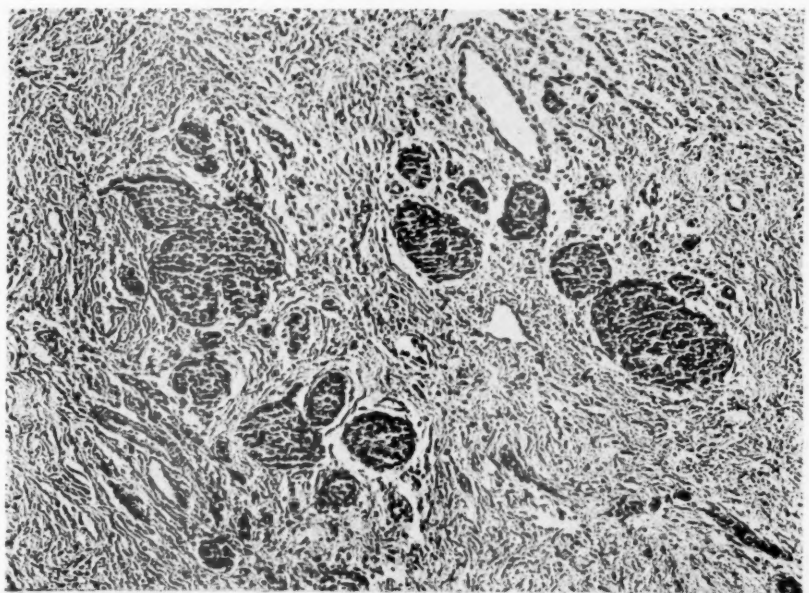


Fig. 5.

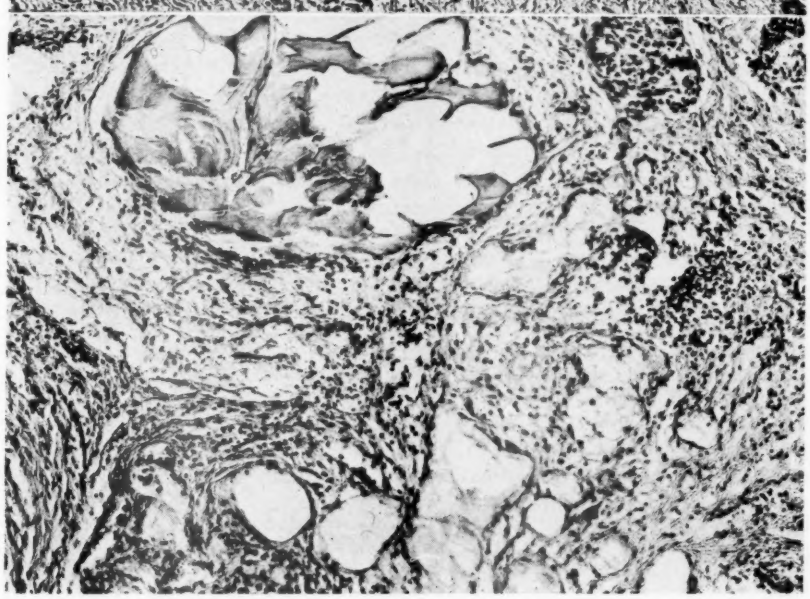


Fig. 4.—Diffuse fibrosis that has obliterated all the parenchyma except for the islets of Langerhans.

Fig. 5.—Cystic dilatation of ducts with some calcareous material still within the lumina.

mouth were given as soon as he could take them; soft diet on the fourth day, and full diet on the fifth day. Penicillin, 50,000 units every three hours, was given for six days. Parenteral fluids were given on the first, second, and third days. On the sixth day acetone appeared in the urine and the patient was given 1,000 c.c. of 5 per cent glucose in saline solution. After that, no further parenteral fluids were given.

No drainage appeared on the dressings after the drainage tube was removed, and the wound healed by first intention.

Two days postoperatively the blood lipase was within normal limits. One week postoperatively the fasting blood sugar was 78 mg. per 100 c.c. A stool was reported as showing a moderate amount of undigested fat. Eight days after operation the glucose tolerance test was normal.

For the first few postoperative days the patient complained of severe burning pain at the site of the incision and deep in the abdomen. This gradually wore away and at the time of discharge on April 13, 1948, he had no complaint except occasional mild pain in the region of the right part of the transverse scar. Bowel movements were regular and the stools were of normal appearance.

Pathologic Report.—

Gross: The specimen consisted of a partially resected pancreas, measuring 8 by 4 by 2 cm. (Figs. 1, 2, and 3). The outer surface was well encapsulated and coarsely nodular. Only the main duct was definitely identified and it appeared dilated and filled with myriads of small, hard, white calculi which formed fairly large masses. On section, the organ consisted of a relatively small amount of opaque, firm, white to tan tissue, arranged in lobules supported in a dense, fibrous stroma. The accessory duct was filled with calculi. Small calculi were found embedded throughout the glandular substance, presumably lying in the duct system.

Microscopic: There was extensive fibrosis that divided the parenchyma into discrete rounded patches. There was a suggestion of regeneration of the parenchyma in the compact insular character of these patches. Islets of Langerhans were present in about normal numbers. The ducts, many of which contained calculi, were distorted, and some organization of exudate had tended to incarcerate the stones and obliterate the lumina (Figs. 4 and 5).

Diagnosis.—Pancreatic calculosis with fibrosis was the diagnosis.

At the time of writing, seven months after the operation, the patient is feeling well. He has no pain, has a good appetite, and has gained seven pounds in weight since leaving the hospital. Stools are normal in appearance and a urinalysis on one occasion showed no glycosuria. He is such an unruly person that it is very difficult to keep in touch with him and have him return to the hospital for follow-up examination, which of course should be made frequently for the rest of his life.

SUMMARY

A discussion of the methods of surgical treatment of pancreatic calculosis and fibrosis is presented, with a report of a case treated with apparent success by subtotal resection of the pancreas.

REFERENCES

1. Eliason, E. L., and Welty, R. F.: Pancreatic Calculi, Ann. Surg. **127:** 150, 1948.
2. Whipple, A. O.: Radical Surgery for Certain Cases of Pancreatic Fibrosis Associated With Calcareous Deposits, Ann. Surg. **125:** 991, 1946.
3. Martin, L., and Canseco, J. D.: Pancreatic Calculosis, J. A. M. A. **135:** 1055, 1947.
4. Rienhoff, F. R., and Baker, B. M.: Pancreolithiasis and Chronic Pancreatitis. Preliminary Report of a Case of Apparently Successful Treatment by Transthoracic Sympathectomy and Vagectomy, J. A. M. A. **134:** 20, 1947.
5. Smithwick, R. H.: Discussion in Whipple, A. O., Ann. Surg. **124:** 1006, 1946.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE PHYSIOLOGIC BASIS OF OPERATIONS FOR DUODENAL, GASTRIC, AND GASTROJEJUNAL ULCER

A REVIEW OF RECENT LITERATURE

HENRY W. MAYO, JR., CHARLESTON, S. C.

(From the Department of Surgery and Gynecology, University of Virginia Hospital)

INTRODUCTION

WITH the increasing complexity of modern civilization, the incidence of gastroduodenal ulceration appears to be on the increase.[245] Peptic ulcer* is most frequently a disease of the third and fourth decades of life, but may occur in infants, or even in the very old.[141, 448] Ivy (1946)[245] stated that between 5 and 12 per cent of the population can be expected to be afflicted with this disease at some period during the life span. Whereas 100 years ago most of the ulcers seen in autopsy material were said to be gastric ulcers, today the great majority of ulcers seen both by the clinician and at autopsy are on the duodenal side. Moreover, there appears to have been a change in sex ratio during the last century; benign ulcers are seen less and less frequently in women, and are becoming much more common in men. This fact is of obvious economic importance, because, by incapacitating the breadwinner of the family, the disease can cause severe economic hardship for that particular group.

Allen and Welch (1942, 1946)[3, 6] estimated that 15 to 20 per cent of the patients admitted to the Massachusetts General Hospital with a diagnosis of duodenal ulcer require surgical treatment sooner or later, and the figures for other institutions are in relatively close agreement. There is a growing feeling expressed by numerous writers on the subject[4, 67, 273, 347, 367, 410, 477, 506] that gastric ulcer, diagnosed clinically, if it does not heal promptly with medical therapy, becomes primarily a surgical problem because of the possibility of the presence of an unrecognized carcinoma. With these considerations in mind, some idea of the frequency of operations for peptic ulcer is obtained, and it becomes immediately obvious that it is extremely important for the gastric surgeon to determine what constitutes a satisfactory operative procedure for benign ulcer. The history of gastric surgery as traced by Finney[152] in 1929, and the profusion of literature on the subject since that time both show that the methods of choice are constantly changing.

The recent reintroduction and popularization by Dragstedt (1943 to 1945),[122, 123, 124] Grimson (1947),[193, 428] Moore and associates (1947)[366, 367, 368]

This paper represents a portion of a thesis presented to the Graduate Faculty of the University of Virginia in Candidacy for the Degree of Master of Science.

*The term "peptic ulcer" will be used throughout to denote gastric, duodenal, and marginal ulcer. While this seems to presuppose a common etiology, it should be borne in mind that they may be different diseases.

of vagus resection as a mode of surgical therapy for peptic ulcer has acted as a strong stimulus for the re-evaluation of all previously used procedures for ulcer in numerous surgical centers.

A further stimulus toward study of the entire subject has been the introduction, by Code, Varco, Wangensteen, and their associates (1940-1942),[92, 212, 490, 494] of an experimental method, consisting of the daily injection of a histamine-beeswax-mineral oil mixture, by which gastric and duodenal ulcers can be produced almost at will in dogs and other experimental animals, without the use of deforming surgical procedures which may cause grave changes in the physiology of the animal. This method has already proved useful, not only in the further study of the etiology of peptic ulcer, but in the evaluation of various surgical procedures used in the therapy of peptic ulcer. It is reasonable to assume that operations which will protect dogs against the histamine-induced ulcer should prove efficacious and perhaps curative in dealing with peptic ulcer in man.

If the surgeon is not to become an artisan who operates at the behest of the internist, it is essential that he understand (1) the physiology of the organs involved, (2) what is known of the etiology and pathologic physiology of the disease he is attempting to treat, (3) what should constitute the most satisfactory procedure in the individual case under consideration, (4) the physiologic and clinical results which such an operation can be expected to produce, (5) the probable mortality rate of the operation chosen, and (6) complications which may ensue, and particularly methods by which those complications may be avoided. With regard to ulcer surgery, these considerations are detailed in a great mass of literature. I felt that it would be of some value to review enough of this literature so that a synopsis could be presented concerning (1) gastric physiology, (2) theories of ulcer genesis, (3) various operations for ulcer, and (4) postoperative physiology. The emphasis will at all times be placed on gastric resection, the operation which has so far withstood the test of time better than any other. Wangensteen, who is unusually well-informed on the subject, has observed that an individual could spend his entire lifetime in the enviable pursuit of reading all the literature dealing with gastric physiology and peptic ulcer. A considerable portion of this literature has been covered, and most of the important ideas dealing with the subject matter outlined here have been assimilated. In this process, numerous contradictions become apparent, both in the physiologic and in the surgical fields, which cause considerable difficulty in an evaluation of this literature. There are a number of reasons for this. A tremendous amount of work has been done on a variety of experimental animals, all of which may not be similar physiologically to man, and some of which (for example, the rat) are certainly not similar to man with regard to gastric anatomy. Particularly in the study of gastric secretion, such a wide variety of test meals have been used, that the results of various workers are not comparable, and the conclusions in many cases not valid. Many observations are uncontrolled, and in some cases there is a possibility that the observations themselves may have been faulty. On the clinical side, a few writers indicate

a lack of knowledge of the basic physiology involved; others overeagerly draw conclusions from insufficient or statistically insignificant data. In some cases, the writings of clinical surgeons tend to be colored by their own pre-existing ideas or prejudices. Thus it should be borne in mind that the literary review to be presented should be accepted with certain reservations.

GASTRIC PHYSIOLOGY

Anatomy and Physiology

The stomach, for practical purposes, may be divided into a (1) narrow cardiac zone just below the cardiac sphincter, (2) a fundus, which consists of the upper convex portion, (3) a corpus, which constitutes the great body of the organ, and (4) a pyloric antrum, which is that narrowed segment just proximal to the pyloric sphincter.

The stomach is a vascular organ and gets its blood supply from four large arteries (the left and right gastric on the lesser curvature, and the left and right gastroepiploic on the greater curvature), all of which originate in the celiac axis. The anastomoses between the many branches of these vessels are numerous, and Layne and Bergh (1943)[297] found that ligation of two or three of the large arteries supplying the stomach of the dog was possible without alteration in the gastroscopic appearance of the gastric mucosa. If all four arteries were ligated, the dogs died of peritonitis resulting from necrosis of the stomach wall. These workers found that ligation of two or three of the large arteries produced no significant change in gastric secretion. On the other hand, LeVeen (1948)[298] found that by ligation of the left and right gastroepiploic, the vasa brevia, and the right gastric artery in dogs, there was some degree of protection against histamine-induced ulcer, and he concluded that the energy requirements for secretion were reduced by the decreased blood flow, thus diminishing the acid secreted. The figures given in his few studies of secretion before and after operation do not appear to be of sufficient significance to support this conclusion. In some dogs, ulceration was produced in the stomach by excessive devascularization. Somervell (1945)[459] has utilized a similar idea as a basis for the advocacy of a partial devascularization of the stomach as an operative procedure useful in the treatment of peptic ulcer. Reeves (1920)[414] made an extensive study of sixty-two fresh human stomachs from autopsy material, with examination of the blood supply of the stomach and duodenum by means of gelatin carmine injection through the celiac axis. He found that the lesser curvature of the stomach and the first inch of the duodenum were less vascular than other portions of these organs, and that in these regions the anatomic arrangement of the smaller vessels is such that there is a pre-disposition to stasis and thrombosis.

The mucosa of the stomach is thrown up into deep folds and rugae, except in the region of the lesser curvature and pyloric antrum, and moves freely over the muscularis. Scott (1929)[444] found that the measured surface area of the mucosa of the average adult stomach was 525 cm. In the lesser curvature region, Aschoff (1924)[20] noted that there were four longitudinal folds, but that

there were no convolutions as in the rest of the stomach, and he called this the "Magenstrasse" or gastric pathway, feeling that this was the normal course taken by a food bolus. Moreover, the mucosa in the lesser curvature and antral region is much more adherent to the muscularis than elsewhere. Wangensteen (1947)[509] felt that these anatomic facts are partially responsible for the occurrence of most benign gastric ulcers in these areas.

The stomach is supplied by parasympathetic nerves (the right and left vagus) and by sympathetic nerves of splanchnic origin. There are two intramural plexuses in the stomach. The myenteric (Auerbach's) plexus contains nerve cells in groups or ganglia connected by nerve bundles containing both intrinsic and extrinsic fibers. The submucous (Meissner's) plexus contains very few ganglion cells, but its fibers communicate with those of the myenteric plexus. Some consideration as to the function of this nerve supply will be given in the discussion on gastric secretion and motility.

There are four types of secretory cells in the gastric mucosa, according to Hollander (1937).[226] The mucous cells of the surface epithelium are thought to secrete a viscous mucus. The peptic cells (chief cells of the body of the gland, central, or adelomorphous cells) secrete proteolytic enzymes. The parietal cells (acid, oxyntic, delomorphous cells, or Belegzellen) secrete hydrochloric acid. The product of the chief cells of the neck of the gland (or mucoid cells) is unknown, although Babkin (1944)[26] felt that they probably secrete a viscous mucoid substance. There is some evidence that, upon occasion, certain of these cells may become transformed to other types of cell. Harvey (1906),[210] by histologic studies, noted that after gastroduodenostomy in dogs, the body chief cells in the region of the anastomosis were transformed into mucous-forming cells. One month after operation a reversal of this transformation occurred.

These various types of secretory cells are not uniformly distributed throughout the gastric mucosa. Harvey[210] noted that there were no parietal cells in the pyloric antrum of the canine stomach. Miyagawa (1920)[364] studied the exact distribution of the various types of cells in human stomachs. He noted that there were three types of gastric glands: (1) The cardiac glands, which secrete chiefly mucus, and contain only a few parietal and peptic cells, are limited to a narrow area immediately around the esophageal orifice. (2) The pyloric zone, the area of which could be determined by describing an arc, the center of which was at the pyloric end of the lesser curvature, with the radius equal to 3/10 of the length of the lesser curvature, contains glands which consist chiefly of mucus-producing cells with only a few oxyntic cells. Miyagawa doubted if the latter secreted any acid. (3) The fundic glands contain all types of secretory cells. Berger (1934)[55] made a thorough study of the exact distribution of parietal cells in the human stomach, and found that there were practically none in the pyloric zone, the greatest number in the major portion of the fundus, while in the upper portion of the fundus and the cardia the number of parietal cells is considerably reduced (Fig. 1). Aschoff (1924),[20] like Berger and Miyagawa, observed that the pyloric zone extends a considerable distance further on the lesser curvature side than it does on the greater curvature side, and noted an

intermediate or transition area between the pyloric and fundic zones. This and other work has been summed up by Babkin (1944)[26] in the schematic representation in Fig. 2. This histologic evidence has received abundant support in the experiments of Ivy (1919),[239] Ivy and Oyama, (1921)[252] and Lim and Dott (1923),[308] all of whom worked with isolated pyloric segments in dogs and found that the secretion of such a segment was thick, viscid, and slightly alkaline (pH 7.0 to 7.5). Ivy and Oyama noted no substance of digestive importance, but Lim and Dott observed some evidence of proteolytic activity (pepsin) in the pyloric secretion. By utilizing innervated and denervated pyloric pouches, these workers were able to conclude that the pyloric secretion was mediated to some extent through the vagus nerve. McCrea and McSwiney (1926)[342] also

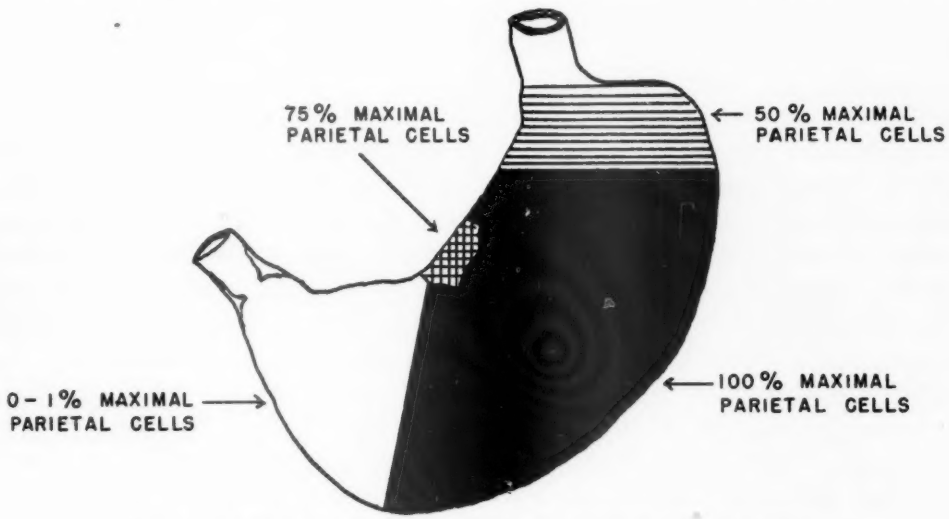


Fig. 1.—Distribution of parietal cells in stomach (after Berger).

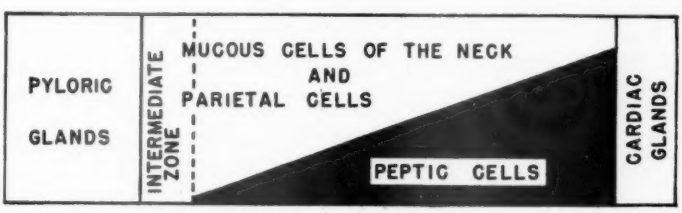


Fig 2.—Schematic drawing of distribution of different types of cells in the gastric mucosa (after Babkin).

studied the secretion of isolated pyloric segments in dogs, after sectioning the vagi in the neck, and determined by the use of variable stimuli to the distal cut ends of the vagi that, depending on the strength of the stimuli, secretory activity was augmented or inhibited. Curiously, despite this incontrovertible evidence, an occasional article is encountered[106, 266] in which the claim is made that by doing a partial or subtotal gastrectomy all the acid-secreting tissue is removed from the stomach.

Gastric Secretion

While the secretion of hydrochloric acid by the parietal cells has been studied in great detail, the other components of the gastric juice have not been

studied so thoroughly. The alkaline component consists chiefly of pepsin, mucus, rennin, and lipase.[534] For a comprehensive review of the subject, including details of physicochemical and histochemical studies, the reader is referred to the excellent work of Babkin (1944).[26] Schiffrin and Ivy (1942)[440] have reviewed the subject in a more concise manner. With regard to the existence of an interdigestive or continuous secretion, the opinion is not uniform. Concerning the digestive period of gastric secretion, all authorities are in agreement that it may be divided into cephalic, gastric, and intestinal phases.

Interdigestive or Continuous Secretion.—Pavlov (1910)[397] in his studies on dogs with gastric fistulas felt that there was no secretion of acid gastric juice except in response to psychic stimuli or food. He observed that great pains were necessary to avoid any psychic stimuli, and thus achieve absolutely basal conditions. Carlson (1923)[85] determined in a man with a gastric fistula that there was a continuous fasting secretion of 10 to 60 c.c. per hour; he felt that there was no true hypersecretion, but that apparent hypersecretion is due to pyloric dysfunction. Wolf and Wolff (1943)[534] found that the fasting stomach of their fistulous subject secreted acid juice at a constant rate (10 to 15 c.c. per hour). Winkelstein (1935),[532] studied the secretion of gastric juice at night in a large number of normal individuals and individuals with benign ulcer, and found that the normal subjects secreted little or no hydrochloric acid during the night, while those with ulcer secreted a large volume of highly acid juice. Dragstedt made similar observations[118, 119, 123] and ascribed the beneficial effect of vagus resection to a diminution of this excessive interdigestive secretion. Thornton, Storer, and Dragstedt (1946)[478] have shown that it is tremendously reduced after vagus resection. Babkin (1944)[26] noted an interdigestive acid secretion in normal individuals who were shielded from psychic stimuli of any sort. To some extent, this idea is supported by Ivy (1941)[243] and Schiffrin and Ivy (1942),[440] who noted that the interdigestive secretion is abolished in normal individuals by the use of atropine. It is interesting that the "hypernormal" secretion of ulcer patients is not abolished by the use of this drug, which makes Ivy feel that possibly this immoderate secretion is due to the excessive production of histamine by irritated gastric mucosa. Bloomfield (1940)[66] has observed that patients with duodenal ulcer secrete under basal conditions a larger volume of highly acid gastric juice than is ever obtained by normal individuals. Recently, Sandweiss, Sugarman, and Podolsky (1946)[438] have made similar observations, but conclude that this is due to delayed emptying of the stomach.

The Psychic (Cephalic) Phase of Gastric Secretion.—The classic experiments of Pavlov (1910)[397] and his group on dogs with esophagotomies and gastric fistulas showed quite conclusively that acid gastric secretion occurs in approximately five minutes in response to the sight, smell, or taste of food, and even to such conditioned stimuli as the appearance of the attendant who customarily fed the animals. However, they were able to demonstrate quite dramatically that by section of the vagi, this psychic secretion was abolished, thus proving that it is mediated through the vagus nerves. Carlson (1923)[85] called this psychic secretion the "appetite juice." This phenomenon was noted by Beau-

mont, and studied in detail by Wolf and Wolff (1943),[534] who found that this psychic secretion was profoundly influenced by the emotional state of the fistulous subject studied. Thus, fear caused a hypoemia of the gastric mucosa and hyposecretion, while resentment or embarrassment caused a hyperemia of the gastric mucosa and hypersecretion. This psychic phase of secretion is extremely variable, depending on the individual and the type of stimulus,[440] but Ivy (1941)[243] believed that an average volume of this secretion is 50 to 150 c.c. during a period of twenty minutes. Vineberg (1931)[491] felt that the various secretory cells were supplied by different fibers of the vagus nerve, since he found that the secretion of various elements was activated at different thresholds of electrical stimulation of the vagi in dogs. Vineberg and Babkin (1931)[492] found that pilocarpine (a parasympathetic stimulator) activated chiefly the production of the inorganic substances and enzymes of the gastric juice, while administration of histamine in conjunction with pilocarpine was necessary to produce a relatively "normal" secretion. Baxter (1932, 1934)[42, 43] studied the role of the sympathetic nervous system in gastric secretion in dogs and cats, and concluded that the splanchnics have a very definite relationship to the mucoid elements of the gastric mucosa, but play no essential part in the cephalic phase of secretion.

Hartzell (1929)[209] sectioned the vagi of dogs in the thorax, and found that there was a marked reduction in the free and total acidity of the gastric secretion after this procedure. In view of the present popularity of vagus resection, Vanzant's work (1931)[487] is worthy of note. Using some of the same dogs that Hartzell had vagotomized two and one-half years previously, she found that the secretion in all four of the dogs studied had returned to approximately normal levels. She postulated that the stomach developed a degree of autonomous control, the mechanism of which was unknown. Likewise, Shapiro and Berg (1934),[449] after making Pavlov (innervated) pouches in dogs for use in the analysis of the gastric secretion, did subtotal gastrectomy with complete division of the vagi below the diaphragm. They found a temporary diminution in the acid secretion of the pouches, which lasted twelve to thirty-three days, but subsequently this secretion returned to normal levels. This was thought due to an autonomous gastric compensatory mechanism, the seat of which was in the plexuses of Meissner and Auerbach.

The possible influence of the parasympathetic nervous system on ulcer development, and its direct clinical application, will be discussed in more detail later.

The Gastric Phase of Secretion.—With the actual arrival of food in the stomach, the second, or gastric phase of secretion is initiated. In normal man, Ivy (1941)[243] stated that this averages 225 to 350 c.c. for a period of approximately five hours, but it may vary considerably in different individuals[68] with regard to acidity and volume. There is practically no absorption of foodstuffs in the stomach, and the quality of gastric juice varies considerably with the type of food. Thus, as Pavlov[397] showed years ago, a protein meal will call forth a higher volume and acidity than a meal composed chiefly of carbohydrates.

Pavlov found that secretion of gastric juice was not stimulated by mechanical irritation of the mucosa or distention of the stomach wall, and similar observations have been made by Wolf and Wolff (1943)[534] on their subject with a gastric fistula. Other authorities, such as Schiffrin and Ivy (1942),[440] quoted work in which gastric secretion was provoked by mechanical distention of the stomach with balloons. The secretagogue effect of food may be the result of substances present in the food (especially in lean meat, liver, etc.) or those arising as products of digestion, such as peptones and fatty acids. Babkin (1938)[25] felt that gastric secretion is in part due to the vagal impulses as a result of cerebral stimulation due to the hypoglycemic state of a hungry individual, but this phenomenon should better be considered as a part of the psychic phase of secretion. As the stomach empties, the gastric and intestinal phases of secretion overlap to some extent. The possibility of the existence of a hormonal mechanism in the gastric phase of secretion is of such clinical and surgical importance that this will be considered in greater detail.

The gastrin theory: In 1906, Edkins[131] found that extracts of the pyloric mucous membrane of cats and pigs, made by boiling with dilute hydrochloric acid, when injected intravenously into an animal, led to secretion of acid gastric juice. Extracts of the fundic mucosa, however made, did not have this property. Moreover, the secretion produced by these extracts could not be diminished by the administration of atropine. He postulated that the pyloric mucosa contained a substance, which he called gastrin, which was liberated into the blood stream as a result of the action of foodstuffs, and thus produced acid gastric secretion. The experiments of Edkins touched off a physiologic controversy which is, as yet, far from settled.

Edkins and Tweedy (1908)[132] inserted pulley-shaped balloons into the stomachs of cats. By tying a ligature around the stomach over the groove of the pulley, they separated the pyloric region of the stomach from the fundus. In acute experiments, using cannulas, they were able to demonstrate that meat extracts and other substances, when introduced into the duodenum or pyloric portion of the stomach, caused a marked secretion of acid juice from the fundus, but when similar substances were introduced into the fundus, there was no evidence of secretion. Gross (1906),[195] working in Pavlov's laboratory, came to similar conclusions.

Popielski[402] called attention to the general distribution in numerous tissues such as brain, gastric and intestinal mucosa and pancreas, and the presence in Witte's peptone, of substances which cause vasodilatation when injected intravenously, and which also cause a more active secretion of all the digestive glands in general. He called such a substance vasodilatin, and thought that the secretagogue effect was due te vasodilatation and not to a specific effect on the secretory cells. Popielski explained Edkins' negative findings with extracts of fundic mucosa as being the result of an overdose of vasodilatin. Keeton and Koch (1915)[263] found a similar substance in the brain, throughout the gastric mucosa, and in smaller concentrations in the duodenum. Injection of this substance would produce a fall in blood pressure. This substance was assayed

using animals with Pavlov gastric pouches and they concluded that it caused true gastric secretion rather than a secretion resulting merely from vasodilatation.

Pavlov (1910)[397] accepted Edkins' theory, and his work was further substantiated by the work of Lim (1922).[306] It was shown by Lim and Ammon (1922)[307] that if pyloric extracts were injected into the portal vein, the secretory effectiveness was less marked, apparently due to a removal by the liver of a portion of the gastrin. Ivy and Whitlow (1922)[254] felt that the experiments of Edkins and Tweedy were uncontrolled, and on repeating them, with modifications, they obtained negative results. Using animals provided with a Pavlov pouch and a small pyloric pouch, both of these being separated from the main stomach, these authors were unable to obtain any increased secretion from the Pavlov pouch when test meals were inserted in the pyloric pouch.

However, at a later date, Ivy and his co-workers (1925)[250] felt that they had demonstrated, by means of cross-circulation experiments between starved dogs and recently fed dogs, both with and without the injection of gastrin, that a humoral mechanism was probably concerned in the genesis of gastric secretion. This humoral mechanism was demonstrated more conclusively[247] by means of the transplantation of a fundic pouch to the subcutaneous tissue, with severance of the normal blood supply after blood supply had developed from surrounding tissues. When such a dog was fed, there was an increase in the volume and acidity of the pouch secretion. However, it was noted that the stimuli had to be more intense to evoke secretion than those necessary with a Pavlov (innervated) or Heidenhain (denervated) pouch.

Some doubt was cast on Edkins' hypothesis by Portis and Portis (1926),[404] who did subtotal gastrectomies on dogs previously provided with Pavlov pouches, and found that the pouches continued to secrete a considerable amount of acid juice. Wilhelmj, O'Brien, and Hill (1936)[528] compared the acid secretion of two dogs before and after partial gastrectomy with that in two dogs before and after gastroduodenostomy. Their experiments, as well as those of McCarthy,[340] indicated that removal of the pylorus lowered the acid secretion more than could be accounted for by the diluting and neutralizing effect of the duodenal secretions. Moreover, a comparison of the gastric secretion from four animals with whole stomach pouches including the pylorus, with that from five animals in which the pyloric antrum had been removed from the pouch, showed that the acid secretion was markedly lowered by removal of the antrum. Enderlen and Zuckschwerdt (1931)[142] noted that one year after resection of the antrum in dogs the second phase of gastric secretion had returned to normal levels. They thought that a readjustment occurred whereby the small intestine took over the function of the pylorus.

Priestley and Mann (1932),[409] working with dogs, did a transection of the stomach, thus excluding the antrum, accompanied by a gastrojejunostomy. At a later operation, the antrum was resected. Observations were made on gastric acidity before and after each procedure. While the first procedure lowered acidity somewhat, the second procedure had no effect on acidity, and they there-

fore concluded that in dogs the pyloric mucosa was not an important factor in gastric acidity. These same workers prepared one series of dogs by isolating pyloric pouches, making gastrojejunostomies, and establishing fistulas to both the fundus and pyloric pouch, by using antiperistaltic segments of ileum. Another series of animals was prepared in the same way except that a fundic pouch was also created and transplanted to the exterior. In the first series of animals, beef extract placed in the pyloric pouch caused secretion in the fundus (although they attributed this to the psychic influence of smelling the extract). In the second series, this did not occur. In both series of animals, hydrochloric acid or gastric juice placed in the pyloric pouch failed to evoke any secretion from the fundus. It is unfortunate that they chose these substances as test meals, since, as will be developed in this paper, acid exerts a very definite inhibitory effect on gastric secretion.

Klein (1932)[275] prepared a gastric pouch from the mucous membrane and submucosa of the stomach, and transplanted it into the subcutaneous tissue, where it developed a new blood supply. Such a pouch, although devoid of vagus or sympathetic innervation, without its normal blood supply, and denuded of Auerbach's plexus, responded to the presence of food in the main stomach by the secretion of gastric juice containing pepsin and hydrochloric acid, thus indicating a hormonal influence. Lewis (1938)[299] excised the antral mucosa in dogs, making an anastomosis between the mucosa of the corpus and that of the duodenum, without removing any of the muscular or serous layers. He found that after such a procedure there was a marked diminution in acid response to a test meal, although the emptying times remained the same. Edkins' hypothesis was further supported by the work of Babkin (1934)[23] who, in experiments with pyloric pouches, obtained results diametrically opposed to those of Priestley and Mann. Also in dogs equipped with Pavlov pouches, gastric fistulas, and duodenal fistulas, with separation of the antrum from the remainder of the stomach, introduction of meat extracts into the fundus failed to produce secretion from the pouch or fundus, but if similar dogs were prepared with the whole stomach separated from the duodenum (that is, without separation of the antrum), the secretory response of both Pavlov pouch and main stomach was strong in response to the ingestion of the same materials. Morrison (1938),[369] using neutral red as a specific test of oxyntic cell activity, concluded that this activity is regulated by a pyloroduodenal hormone.

Sacks and others (1932)[429] have shown that the gastric secretory effectiveness of acid extracts of the pyloric mucosa of dogs is inactivated by histaminase, and they concluded that histamine is the sole secretory excitant in so-called "gastrin" preparations. However, they emphasized that they had not proved that histamine was the gastric hormone, nor was it proved beyond doubt that there was a gastric hormone. Histamine has been isolated from the stomachs and intestines of several animals[60] and from the gastric mucosa (both fundic and antral) in men.[481] Babkin (1934)[23] has shown that secretin and histamine are not identical, but gastrin and histamine have not been separately identified chemically.

The experiments of Gregory and Ivy (1941)[188] with dogs with two and three gastric pouches demonstrate conclusively that a hormonal or humoral factor is concerned, but they found that the pyloric mucosa was not the sole site of the hormone, since the presence of secretagogues in the fundic pouch caused acid secretion in the pouch transplanted to the subcutaneous tissue. The possibility must not be overlooked, in these and many similar experiments, that the "fundic pouches" may have contained small areas of antral mucosa. Recently Komarov (1942)[282] has repeated Edkins' first experiments with almost identical results.

From this mass of experimental evidence, it seems valid to conclude only that there is a humoral mechanism concerned in gastric secretion. Whether the hormone is identical with histamine, and whether the hormone is localized chiefly to the pyloric mucosa, remains to be determined. There certainly is considerable clinical evidence supporting Edkins' thesis. At least we know that patients with a Finsterer exclusion resection without removal of the antral mucosa tend to develop jejunal ulcer[3] or the "antral syndrome."[367] Wangensteen,[506, 512] after a study of the experimental and clinical evidence, accepted the gastrin hypothesis chiefly as an augmenting factor in gastric secretion, but not as an initiating factor, and noted[296] that some doubt is cast on such a theory by the development of jejunal ulcers after pylorectomies.

The Intestinal Phase of Secretion.—Ivy and McIlvain (1923)[251] prepared Pavlov pouches in dogs, and at a later date made fistulas by transecting the duodenum distal to the pancreas and transecting the jejunum distal to the ligament of Treitz; one end of this segment of bowel was brought out through a stab wound to the body surface and the other end closed; continuity of the gastrointestinal tract was re-established by a duodenojejunostomy. They studied the secretion of the Pavlov pouches obtained in response to substances introduced into this intestinal fistula, and found that acid secretion was evoked by a considerable variety of substances, thus proving the existence of an intestinal phase of secretion. This phase has been studied in a slightly different manner by Ivy, Lim, and McCarthy (1925).[249] They found, in a dog in which the entire stomach was formed into a pouch and continuity re-established by an esophagoduodenostomy, that the feeding of secretagogues by mouth resulted in acid secretion from the total gastric pouch after a latent period of 1 to 3 hours. On the other hand, undigested food would not stimulate such a secretion, and it is generally agreed that gastric secretion in the intestinal phase is due to the secretagogue action of the products of digestion (such as peptones and amino acids). As previously stated, the intestinal phase overlaps the gastric phase to some extent, and the intestinal phase may last a considerable period of time, depending on the type of food. With a high protein diet, the intestinal phase of secretion may amount to 2 to 3 liters per day.[440] There is some evidence that the intestinal phase is mediated through the vagi, since it is inhibited by the administration of atropine.[26]

The Control of Gastric Acidity.—There are a number of quite different theories of the mechanism by which hydrochloric acid is secreted in the stomach,

most of which are mentioned by Babkin (1944),[26] along with the physicochemical evidence involved. Perhaps the two most important are those of Rosemann (1907)[421] and Pavlov (1910).[397] Rosemann thought that the total chloride of the gastric juice was constant, but that the acidity was variable in the juice as secreted. This variability in acidity was thought due to (1) an accumulation of neutral chloride in the gastric mucosa and (2) a formation of hydrochloric acid from the neutral chloride. The oxyntic cells were assigned (by Rosemann) the capacity of concentrating chloride to a higher level than that in the blood or lymph and then combining it with H + ion. In true anacidity, he thought the total chlorides were secreted in the form of neutral chloride.

The theory more generally accepted by physiologists today is that of Pavlov, who held that the gastric juice, as secreted, always possessed the same degree of acidity, 0.5 per cent or .16 N HCl, which is isotonic with the blood. Babkin,[21] Dragstedt,[121] Hollander,[227] Wilhelmj,[526] Wolf and Wolff,[534] and other eminent physiologists are in essential agreement with this theory. The details of how this idea was arrived at need not concern us here.

If it is true that the hydrochloric acid in dog and man occurs at a concentration of 0.5 per cent, how can it be explained that the average acidity of gastric contents is found[21] to be in the neighborhood of 0.2 per cent HCl? Moreover, it is known[18] that after the initial secretory period there is a rapid fall in acidity, and this merits some explanation. Pavlov[397] observed that "the first duty of intestinal digestion is to convert the acid medium of the stomach into an alkaline or neutral one in the bowel." Boldyreff (1914)[71] went further than this, and elaborated a theory as to the "self-regulation of gastric acidity." As a result of experiments on dogs in which 0.5 per cent HCl was introduced into the stomach, followed by the collection of gastric and duodenal juice through fistulas, he thought that the acidity of the gastric juice, constant at 0.5 per cent HCl as secreted, was quickly lowered to a level between 0.15 and 0.2 per cent HCl, this partial neutralization being due chiefly to a reflux into the stomach of alkaline juices from the duodenum. The pancreatic juice was thought to be most important as a neutralizing agent, since the prevention of the entrance of bile (by cholecystoenterostomy and ligation of the common duct) or of saliva (by means of an esophageal fistula) into the stomach resulted in very little change in neutralization of the acid test meal. When the pancreatic ducts were ligated, the body responded with an excessive flow of bile and succus entericus to aid in neutralization. Boldyreff also found that when neutral or alkaline fluids were introduced into the stomach, the organ responded by an excessive secretion of acid to bring the acidity up to normal levels.

This theory has received considerable opposition in certain quarters. MacLean and Griffiths (1928)[316] concluded, as a result of acid test meals and fractional analyses in human subjects, that the gastric glands secrete at all times a juice of constant chloride concentration in which the relative amount of basic (Na^+) and acid (H^+) ions in combination with the chloride ion were varied according to the requirements of the stomach. This differed but little

from the theory of Rosemann. They discounted the possibility of regurgitation of duodenal contents as an important factor in neutralization because of the absence of trypsin in most specimens of gastric juice. To quote their work: "The presence of a certain concentration of acid in the stomach inhibits secretion of acid, with the result that a neutral fluid containing chloride is secreted, which, by dilution, reduces the acidity of the gastric contents." The studies of Griffiths (1936),[192] with tubes in both stomach and duodenum, showed that the secretion of acid by the stomach was inhibited by the introduction of weak hydrochloric acid into the duodenum. It was suggested that the acidity of the gastric contents entering the duodenum may be the important factor in the control of gastric acidity during the normal digestion. Shay and others (1942)[453] came to similar conclusions. McCann (1929),[337] in his studies on emptying time, felt that he had disproved Boldyreff's theory of alkaline regurgitation. He thought two factors were responsible for neutralization: (1) a gradual reduction of the established high rate of secretion of acid to a low one; and (2) the capacity of the constant basal secretion of mucus to combine with a constant fraction of the changing volume of acid secreted.

Shay and his co-workers (1932)[454] studied human subjects by administering bromsulfalein intravenously, followed by an acid test meal and fractional analysis. They found that while duodenal regurgitation does take place, there was no correlation between the concentration of dye in the stomach and the reduction in acidity, and the conclusion was therefore reached that Boldyreff's theory lacked validity. This theory was further questioned by Kesavalu and Mann (1943),[270] who isolated the duodenum in dogs, and closing one end, drained the other end by anastomosis to the fundus, re-establishing continuity by a gastrojejunostomy. On comparing acid values of fundic pouches or of the stomach (by means of antiperistaltic fistulas made from loops of ileum) before and after such a procedure, they found that the acidity of the fasting stomach was not reduced by this procedure, although bile was always found in the stomach, and in many cases the volume and acidity of gastric secretion was higher than it was before. Since the entire duodenal contents could not cause effective neutralization and buffering of the gastric secretion, they doubted that regurgitation of duodenal contents was an important mechanism in neutralization of gastric acidity.

However, the evidence in favor of this mechanism is considerable. A study was made of the trypsin in the fasting gastric contents of thirty-four human subjects by Spencer, Meyer, Rehfuss, and Hawk (1915),[460] who found trypsin absent in only two of the thirty-four individuals. Moreover, with the introduction of acid into the stomach of these patients, the trypsin values immediately rose, but when water or alkaline solutions were introduced, the tryptic values remained low. The tryptic enzyme was thought to be regurgitated from the duodenum. The importance of pyloric relaxation in this regurgitative phenomenon was emphasized by Bolton and Goodhart (1922),[75] who noted that in ulcer patients with pylorospasm, or with pyloric stenosis, such regurgitation failed to occur, resulting in hyperacidity. In normal individuals, as the curve

for hydrochloric acid concentration went down, the curve for inorganic chlorides went up, presumably due to regurgitation and neutralization by duodenal juices, but this was not so apparent in ulcer patients. Antiperistaltic movements of the duodenum promoting regurgitation of duodenal contents has actually been demonstrated[74, 77] by roentgenologic means.

Burget and Steinberg (1922),[81] working with dogs, found that regurgitation of duodenal contents into the stomach occurred regularly within thirty to forty-five minutes after introduction of 100 to 150 c.c. of 0.5 per cent HCl, and the acidity of the stomach contents was reduced to 0.1 to 0.15 per cent HCl in seventy-five to ninety minutes. Apperly (1926),[17] studying the control of the pylorus, thought that any chyme propelled into the duodenum which was not of a certain acid and salt value was promptly regurgitated back into the stomach until that value was reached. Rehfuss and Eads (1929),[415] employing balloons in both the stomach and duodenum of medical students, observed that in fasting stomachs there were periods during which increased duodenal tonus and increased motor activity in the duodenum were conducive to regurgitation. This activity did not correspond to that of the antrum. Evidence of early duodenal regurgitation was found in seventy-two per cent of forty-six subjects on whom fractional analyses after acid test meals were performed by Apperly and Norris (1930).[18] These authors attributed more importance to the factor of dilution than to the factor of neutralization in the lowering of gastric acidity.

It is known that deviation of the duodenal contents to the lower gastrointestinal tract, by preventing such a regurgitative phenomenon, results in an elevated gastric acidity[525] in dogs. The role of the pylorus in this process of regurgitation was dramatically demonstrated by the experimental work of Elman and his group (1931, 1933).[136, 140] If pyloric insufficiency was produced by cutting the sphincter, a persistent lowering of gastric acidity followed, and there was augmented neutralization of acid test meals administered to the dogs. On the other hand, when partial stenosis of the pylorus was artificially produced, the acid test meals administered to these dogs were incompletely neutralized. Ivy, Droegmueller, and Meyer (1927)[246] obtained essentially similar results with artificial pyloric stenosis in dogs. Medoff and his colleagues (1941)[349] were unable to demonstrate consistently any change in acid values after producing partial pyloric obstruction, but their work was seemingly invalidated by their own observation that the emptying time of these supposedly obstructed stomachs was not materially affected.

While theorizing as to the important mechanism in the control of gastric acidity, whether it be a result of the regurgitation of duodenal contents or an expression of a variability in the acid concentration of the gastric juice as secreted, it is well to remember that there are other less important mechanisms concerned in the dilution, neutralization, and buffering of gastric acidity. The volume output and rate of gastric emptying are obviously important.[440] Hollander (1937, 1938)[226, 227] believed that a "dilution secretion" of nonacid fluid, with a composition similar to blood plasma, occurs from the neck chief cells. This theory is not widely accepted, however. Saliva and certain foodstuffs have

a moderate neutralizing power, and protein foods may bind up hydrochloric acid as combined acid.[21] The importance of mucous secretion as a neutralizing agent has received some prominence.[26, 76] MacLagan (1934),[315] in a statistical analysis of 389 fractional test meals, concluded that reduction in gastric acidity was due chiefly to the neutralization and dilution produced by the alkaline mucous secretion of the pyloric segment. Helmer (1934)[215] thought mucus to be present in sufficient quantities in the gastric contents to account for the main variations in gastric acidity. This evidence has been utilized by Fogelson (1931)[159] as a rationale for his advocacy of the treatment of peptic ulcer by the administration of mucin. Kim and Ivy (1931)[272] have prevented the development of duodenal ulcers in dogs with biliary fistulas by the administration of mucin.

Inhibition of Gastric Secretion.—Inhibition of gastric secretion may occur as a result of nervous, humoral, or chemical stimuli, or as a result of certain abnormal factors. Wolf and Wolff (1943)[534] have shown quite well in their fistulous subject that certain emotional states, such as fear, inhibit gastric secretion. Both the vagi and splanchnics contain inhibitory fibers, through which such impulses are mediated. It has also been shown that excessive mechanical distention of the intestine will inhibit secretion from the stomach. Atropine has been found to decrease the volume of secretion resulting from histamine stimulation in man, but does not affect the free acid concentration to any great degree.[403] Roberts (1925)[418] thought that part of this effect was due to parasympathetic inhibition. He found the free acid concentration reduced after atropine, and this was thought due to relaxation of the pylorus and, thus, increased regurgitation of duodenal contents.

Pavlov (1910)[397] recognized that a fatty meal inhibited gastric secretion and prolonged the emptying time. Kosaka and Lim (1930)[284] demonstrated that the probable mechanism of this inhibition was the formation in the mucosa of the small and large intestine, following contact with fat, of an inhibitory substance which they called enterogastrone. Potent extracts of the duodenal mucosa have been prepared[183] which will inhibit gastric secretion in dogs, and hope has been expressed that such substances will prove valuable in the medical treatment of peptic ulcer in man.[185] A similar substance, called urogastrone, which has been prepared by Ivy's group (1940),[184] is found to reduce the human gastric secretory response to histamine with regard to volume, acidity, and free acid.

It has been demonstrated by MacLean and Griffiths (1928, 1936),[192, 316] that introduction of acid into the stomach inhibits the secretion of acid. These authors also noted that introduction of acid directly into the duodenum inhibited gastric secretion. These results were confirmed by Day and Webster (1935),[105] who thought that this acid inhibition was an important mechanism in the regulation of gastric secretion. The latter group of authors found that the intestinal phase of secretion was not inhibited by N/10 HCl in the stomach, but inhibition resulted when the acid entered the duodenum. Stevens, Segal, and Scott (1940)[470] found that there was no effect upon gastric secretion when dilute

hydrochloric acid was introduced directly into the duodenum, but the mechanism has been generally accepted by most authorities. This acid inhibition is known to fail[440] in the presence of excessively strong secretory stimuli, and particularly in the presence of the cephalic phase of secretion, and it is therefore thought that a nervous rather than a humoral mechanism is concerned.

Andrus, Lord, and Stefko (1942-1944)[13-16, 312, 313, 463] found that in dogs perfusion of the stomach with washings from an isolated jejunal loop caused a profound depression in the volume and acidity of gastric secretion. Moreover, they found that when a segment of jejunum was implanted into the wall of the stomach, keeping its blood supply intact, the pH of the gastric mucosa rose, and the secretory response to histamine was reversed (that is, the volume and acidity of the secretion diminished instead of increasing). The effect was greater than could be accounted for by neutralization of acid with the alkaline jejunal secretion, and it was thought to represent some type of inhibition of some phase of gastric secretion in which histamine played an important role. The exact mechanism concerned was not determined, although Andrus felt it was not enterogastrone. This procedure was found to protect against histamine-induced ulcer in dogs, although the series of dogs so tested was quite small. The experimental results were so promising that the pedicled jejunal graft was used as a mode of surgical therapy in a small number of ulcer patients, and the immediate results were gratifying with reduction in acidity in three of four cases. However, in the preliminary reports, none of these cases were followed more than nine weeks. The hope aroused by this work that such an operative method could be used as a means of producing inhibition of gastric secretion was promptly ablated by the work of Grossman, Dutton, and Ivy (1945),[197] who found that neither perfusion of a gastric pouch with jejunal washings nor implantation of the pedicled jejunal patch into the gastric wall resulted in any significant change in the acid secretory response to histamine. Andersen, Slutzky, and Moertz (1945)[11] obtained similar results in their dogs. The results of Andrus and his group were also negated by Kolouch, Dubus, and Wangensteen (1945),[281] who found that such a procedure did not prevent the histamine-induced ulcer in dogs, nor did it reduce the secretory response to histamine. Saltzstein and Kurtz (1946)[432] have shown that this procedure fails to prevent the development of ulcer in Mann-Williamson dogs.

In addition to the factors resulting in inhibition of gastric secretion which have already been discussed, there are certain abnormal conditions which depress gastric secretion. The acidity is decreased 85 per cent in pregnancy,[440] and it is interesting to note that peptic ulcer rarely occurs in pregnant women, and if an ulcer is known to be present at the time of conception, the clinical improvement during pregnancy is marked. Hyperglycemia and hypocalcemia apparently inhibit acid secretion, as does deficiency in certain vitamins, particularly thiamine and vitamin C.[440] Radiation of the stomach depresses gastric acid secretion to the point of achlorhydria after histamine,[395] and Palmer (1947)[396] has utilized this as the basis for treating peptic ulcer with x-ray.

The Composition of Gastric Juice.—In addition to hydrochloric acid, which has been quite well studied, the gastric juice in man contains pepsin, mucin, inorganic salts, histamine, rennin, traces of lipase, and the so-called intrinsic factor in the prevention of pernicious anemia.[440] Polland and Bloomfield[400] found that there was no correlation between pepsin output and acidity, and thought their secretory mechanisms independent. Vanzant and her co-workers (1932)[488] studied the gastric acidity from 3,746 cases, and found that there was a tremendous variation in the normal acidity although it tends to decrease with age. Because of this and other work, Alvarez (1943)[9] recently concluded that gastric analysis has little value as a diagnostic procedure except in connection with the anemias. Similar observations were made previously by Bloomfield and Keefer (1926).[68] The analysis of gastric contents with the use of various test meals (Ewald, alcohol, etc.), is somewhat colored by the dilution, buffering, and combining power of the test meal substance. Such an objection is not valid with regard to histamine as a stimulus, and so it may be considered the most reliable indicator of gastric secretion. Alcohol is thought to stimulate chiefly the secretion of hydrochloric acid,[22] while pilocarpine and other cholinergic drugs activate the production of gastric mucus and enzymes. Babkin (1938)[24] believed that stimulation of the vagi results in a liberation of histamine in the gastric mucosa, and the histamine activates the parietal cells. A hypoglycemic state results in the secretion of a juice of high acidity and peptic content, and Babkin felt that the routine use of the insulin hypoglycemic test, as outlined by Hollander (1946)[228] for use in testing the completeness of a vagus resection, would be a more accurate measurement of the gastric secretory capacity.

Pepsin is activated by hydrochloric acid, and is inhibited by products of its own digestion.[440] However, mucus inhibits peptic digestion, possibly due to the adsorption of pepsin. From the standpoint of this work, the minimal digestive activities of rennin and lipase are unimportant.

In summation, to quote Babkin, "the secretory work of the gastric glands, therefore, is not regulated as a whole, but the final product of this activity, namely the gastric secretion, is dependent, especially as regards its composition, on the participation of various mechanisms, nervous or humoral, that stimulate (or inhibit) different parts of each gland."

Histamine and Gastric Secretion.—At this point, since the use of histamine in testing gastric secretory function is so widespread, and since it is used experimentally in the production of peptic ulcer, it may be well to discuss briefly the relationship of histamine to gastric secretion. A thorough review of the physiologic effects of histamine was contributed by Best and McHenry[60] in 1931. Histamine in considerable quantities has been obtained from canine gastric mucosa[173] and from human gastric mucosa.[481] In both species, a secretagogue was found, not only in the pyloric region, but in the fundic mucosa, which was inactivated by histaminase. The possibility that histamine may be identical with "gastrin" has been suggested by Sacks and his co-workers (1932)[429] but has not been proved.

Parenteral administration of histamine results in a highly acid gastric secretion. Lim and his co-workers (1923),[309] and Polland (1932),[399] found that

in human subjects histamine increased the rate of secretion and the amount of both acid and pepsin in the gastric juice. However, Gilman and Cowgill (1930),[175] studying the secretion from Pavlov and Heidenhain pouches in dogs after the administration of histamine, called attention to the fact that there was a progressive decrease in the pepsin concentration in the pouch juice from the level obtained shortly after the administration of histamine. This was thought due to a "washing out" of the glands by the newly secreted acid, the original high level of pepsin being a reflection of the state of secretory activity of the chief cells before the histamine was administered. This work has been confirmed in dogs by Vineberg and Babkin (1931),[492] and in man by Toby (1937).[479] Histamine is thought to act directly on the parietal cells, having a selective affinity for these cells; the secretory response to histamine is not affected by vagotomy or atropine.[60] Some evidence has been presented by Alley (1935)[7] that histamine actually inhibits the action of the vagi on the peptic cells, thus diminishing the secretion of pepsin. Histamine, when prepared in a beeswax-mineral oil mixture, as done by Code and Varco (1940),[91] and administered to experimental animals in doses varying from 15 to 60 mg. daily, will cause a marked increase in the volume and acid of gastric secretion within fifteen minutes after administration. This increased secretion was found by Code and Varco to persist for twenty-four to forty hours, although the maximum level was reached four hours after administration, following which there was a considerable decline.

Motor Physiology of the Stomach

The motor physiology of the stomach is, of course, inextricably bound up with the mechanism of gastric secretion, but for the sake of clarity will be discussed separately. Quigley (1942)[412] has reviewed the subject rather thoroughly. The motor functions of the stomach in relation to food are (1) to store food, (2) to break up the food mechanically, (3) to mix it with gastric juice, and (4) to move it forward. It has already been shown that appetite is a cerebral phenomenon. Appetite is associated not only with the cephalic phase of gastric secretion, but with hunger contractions, mediated through the vagi, which occur as waves of peristalsis, lasting about thirty minutes, passing slowly from cardia to duodenum, and followed by a relaxation period lasting about thirty minutes. These contractions are inhibited by the ingestion of food or by vagotomy, but are augmented by splanchnicotomy.

When food enters the stomach, the intragastric pressure falls with relaxation. The food is held chiefly in the fundus, where it undergoes little mixing, but is gradually reduced to a semiliquid state. Fats are melted, proteins are attacked by pepsin and hydrochloric acid, and starches partially digested by ptyalin. Periodically portions are broken off and pass to the pyloric antrum where they are broken up by powerful peristaltic waves which require thirty seconds to reach the pylorus from the incisura. Fluids usually leave the stomach one to four minutes after ingestion. With other foods, the rate of emptying depends on the character and amount of the food, the activity of the pyloric sphincter, antral tonus, etc. Fatty meals (through the medium of enterogas-

trone) inhibit motility as well as secretion, and require a much longer time (six to seven hours) for emptying than meals poor in fat, which require four to five hours.[534] Other substances, such as excessive amounts of sugar, hydrochloric acid, and peptones may also cause inhibition of gastric peristalsis. Certain emotional states such as worry may also inhibit gastric activity.

Pyloric achalasia, resulting in interference with emptying of the stomach and regurgitation of duodenal contents, is thought to produce stagnation and hyperacidity[412] and is of considerable importance in the pathogenesis and pathologic physiology of peptic ulcer. Interest, therefore, has been centered on the mechanisms by which the pyloric sphincter is controlled. Forty years ago, Cannon (1907)[83] elaborated the theory that the pylorus was controlled by acid concentration—that is, that a high acid concentration in the pyloric antrum would cause opening of the sphincter, and a high acid concentration in the duodenum would cause the sphincter to close. This theory, which was further developed by the work of Apperly (1926)[17] and Shay and Gershon-Cohen (1934),[451] was an attractive one to explain the gradual emptying of the stomach in a normal individual, but as Hurst (1925)[235] pointed out, did not explain why the pylorus is able to function in patients with achylia gastrica, or why pylorospasm occurs in association with gastric hyperacidity. Hurst felt that the hyperacidity was the result of the failure of the pylorus to open, rather than the cause. This subject will be developed more fully in the discussion of the relationship of acid-peptic digestion to ulcer formation.

It is known[380] that vagal stimulation causes contraction of the pylorus while sympathetic stimulation causes relaxation. Thomas and others (1934, 1935)[474, 476] found that acid in the region of the pylorus had little effect on the state of the sphincter, and that the contraction of the sphincter was really a termination of antral peristaltic waves. Thomas thought that gastric emptying was regulated in part by a reflex inhibition of antral peristalsis due to duodenal stimulation. McCann (1929)[338] felt that the products of protein digestion caused inhibition of the sphincter, while undigested protein stimulated contraction. Werle and others (1941)[523] studied pressure gradients between the antrum and duodenum during digestion by means of intraluminal balloons, and concluded, like Thomas, that contraction of the pyloric sphincter represented the termination of an antral peristaltic wave.

THE ETIOLOGY OF PEPTIC ULCER

It can safely be stated, without fear of contradiction, that the cause of gastroduodenal ulcer is unknown. The subject is one which has attracted great interest on the part of clinicians, physiologists and experimentalists, and the constantly increasing volume of literature on the etiology of peptic ulcer attests to the fact that no one theory has been validated to the exclusion of others. A large part of this literature has been reviewed in admirable fashion by McCann (1929),[339] De Bakey (1937),[108] Lannin (1945),[295] and many others. Certain facts are known concerning the incidence of peptic ulcer which have never been adequately explained. Some of these are the increased susceptibility of the male,[245] the fact that in certain families there seems to be a predisposition

toward ulcer,[360] the fact that peptic ulcer is extremely rare in conjunction with either diabetes or pregnancy, the idea that certain constitutional types have a predisposition toward ulceration,[214] and the fact that ulcer is extremely rare as a spontaneous occurrence in lower animal forms,[241] although so common in man.

Nevertheless, as a result of a great variety of clinical and experimental research, a considerable number of factors are thought to play a greater or lesser part in the pathogenesis of peptic ulcer; some of the more important factors will be briefly considered. The factor which has achieved the greatest prominence, especially with regard to ulcer therapy, is the chemical or acid-peptic factor.

The Acid-Peptic Factor

Peptic ulcer occurs only in those parts of the gastrointestinal tract which are bathed by acid gastric juice.[310] In addition to the stomach and duodenum, it may occur in or adjacent to areas of heterotopic gastric mucosa, which is sometimes found in the lower esophagus, or in a Meckel's diverticulum,[19, 310] or it may occur in lower intestinal segments if they are brought into contact with the acid gastric juice. As Rivers (1934)[417] stated, "When tissues other than those naturally accustomed to the chemical and mechanical action of gastric juice are exposed to the aggression of acid chyme, the potentiality for ulceration promptly develops."

The Digestive Power of Gastric Juice.—When the known property of pepsin and hydrochloric acid to digest living tissue is considered, it is really surprising that peptic ulcer is not a universal occurrence. John Hunter felt that the "living principle" prevented digestion by gastric juice, but this was refuted by the classic experiment of Claude Bernard, who immersed the leg of a living frog in the gastric fistula of a dog, and obtained digestion of the leg. It is interesting to note that early in his career, Dragstedt (1917)[117] came to the conclusion that the digestive action of gastric juice was not important in ulcer genesis. Bernard's experiment has since been confirmed by Dragstedt and Vaughan (1924)[125] both in vitro and in vivo. In addition, in dogs, these workers implanted various organs (spleen, kidney, segments of bowel), with blood supply intact, into the anterior wall of the stomach, and found that not only were the organs not digested, but in some cases the implanted organ was covered over by a layer of regenerated tall columnar gastric epithelium. The remarkable regenerative capacity of the gastric mucosa has been demonstrated by Ferguson (1928),[151] who found that large artificially produced defects would heal. It has recently been demonstrated[405] that a hypersecretion of acid gastric juice induced by repeated injections of histamine-in-beeswax will seriously interfere with this process of repair. Katzenstein (1913)[262] found that of various organs implanted into the stomach only the mucosa of the stomach and duodenum were resistant to the digestive action of gastric juice. However, organs implanted in the duodenum, in a more alkaline medium, are not digested.[381] Price and Lee (1946, 1947)[406, 407] implanted a great variety of organs more deeply into the lumen of the stomach than Dragstedt and Vaughan, and found that all of these organs were digested, but once they were covered over by regenerated gastric mucosa, no further digestion occurred. This digestive process

was accelerated by hypersecretion produced by histamine-in-beeswax, to such an extent that the gastric mucosa itself was digested.

If the stomach of an experimental animal is isolated, with blood supply and vagal innervation intact, and the exit of the juice secreted is prevented for a time, Dragstedt (1935)[118] has shown that the gastric mucosa itself will be digested with the formation of chronic perforating ulcers. Similar results have been obtained by Stein, Grossman, and Ivy (1947)[464] with closed Heidenhain (denervated) pouches.

The Role of the Pylorus.—Physiologists agree that a true hyperacidity in the sense of secretion of hydrochloric acid at increased concentration does not occur, but that an apparent hyperacidity may be the result of a hypersecretion of juice of normal acidity or a normal rate of secretion with interference with emptying of the stomach and interference with regurgitation of alkaline duodenal contents.[26] It is natural, therefore, that a great deal of interest should center on the role of the pylorus in gastroduodenal ulcer. Hughson (1927)[233] noted that ulcers produced by excising segments of mucosa remained active twice as long in animals with normal pyloric function as in those in which the pylorus had been defunctionalized by sectioning the circular muscle. Acute ulcers, produced by the submucosal injection of 5 per cent silver nitrate as reported by Friedman and Hamburger (1914),[164] became chronic only in those animals in which partial pyloric obstruction had been produced. In these animals, there was an increase in the acidity of the gastric contents. Elman and Eckert (1933)[136] partially closed the pylorus in dogs with a ligature; one dog developed a perforated duodenal ulcer, the remainder showing a marked duodenitis. The disturbance in the normal acid-alkali relationship produced by partial pyloric stenosis, contrived by wrapping a collar of jejunal muscle with intact nerve supply around the pylorus, was reported by Morton (1934)[376, 377] to cause a duodenitis, similar to that seen clinically associated with duodenal ulcer in each animal studied. In acute experiments, Shay's group (1945)[455] produced ulcers in the rumina of rats by the simple expedient of ligating the pylorus. These ulcers, which occurred seventeen to nineteen hours after operation, were attributed to the presence of a large amount of unbuffered gastric juice. It has been shown[138] that in patients with active peptic ulcer, the neutralization of an acid test meal is slower than normal. Histologic evidence that the pylorus plays an important role in ulcer production was presented by Truesdale (1915),[482] who found that resected specimens from patients with active ulcer showed a hypertrophy of the pyloric musculature.

"Hyperacidity" and Peptic Ulcer.—It is commonly thought that a high acid secretion is the usual accompaniment of benign gastric or duodenal ulcer. In some 2,500 cases of benign ulcer, Palmer (1942)[395] failed to find a single one that had true anacidity to histamine. Studies of the gastric acidity in large series of cases, such as those of Friedenwald (1912),[160] Emery and Monroe (1929),[141] Heintz and Welker (1925),[213] and Palmer (1942),[395] have shown that a patient with benign ulcer may have almost any degree of acidity, but will always secrete some acid. Palmer (1947)[396] found that normal or subnormal

acid was more the rule than the exception in cases of gastric ulcer, although patients with duodenal ulcer usually had a high acid concentration. Vanzant and co-workers (1936)[489] noted that not only the acidity but the pepsin concentration of gastric secretion was higher in most cases of duodenal ulcer than in those cases with gastric ulcer.

While most writers feel that an ulcer may result from a hypersecretion of acid juice, there is a certain amount of experimental evidence to suggest that such a "hyperacidity" is a result, rather than a cause, of the ulcer. Dragstedt and Vaughan (1924)[125] produced chronic ulcers by injecting silver nitrate beneath the mucosa of dogs' stomachs, and noted that gastric acidity rose after development of the ulcers. A similar occurrence has been observed by Cheney (1938)[87] after the production of gastric ulcers in chicks by feeding a deficient diet. Such observations may be explained on a basis of pylorospasm secondary to ulcer. Harper (1932, 1935)[207, 208] connected closed gastric pouches of dogs to the body surface by interposing loops of small bowel, with blood supply intact, arranged in an antiperistaltic fashion. Ulcers, many of which perforated, developed in these loops of bowel, since the peristalsis of the bowel prevented egress of the gastric secretion, and, on studying the acid content of the pouches it was found that as the ulcers developed, the acidity rose, but not before. However, in those preparations in which a pyloric pouch was utilized, and in which no acid secretion occurred, no ulcers developed.

This problem has been attacked in a different fashion, by studying the reaction of the duodenal contents. The reaction of the isolated duodenum in the dog is quite constant,[238] with an alkalinity of pH 7.10 to 8.15. However, Mann and Bollman (1935),[327] characterizing the duodenum as the "chemical battleground of the gastrointestinal tract," have observed that the reactions of the intact duodenum in continuity with the rest of the gastrointestinal tract may fluctuate remarkably. When highly acid values were found in the stomach of dogs equipped with Mann fistulas, the duodenal content was also found to be acid, although normally it was just on the alkaline side of neutrality.[325] Stevens (1935)[469] demonstrated the capacity of the duodenum to neutralize, buffer, and dilute acid solutions perfused through it. Thomas and his co-workers (1940, 1942),[58, 475] cannulating various portions of the gastrointestinal tract in dogs, found that at the height of the acid secretory curve in the digestive process the pH of the duodenal contents was rarely less than 3.0 and usually nearer 4.0.

A comparison made between the duodenal contents of relatively normal patients and of patients with peptic ulcer, by Morton (1929),[375] using two tubes, the position of which was checked by x-ray examination, showed that there was no free hydrochloric acid in the duodenal contents in the ulcer-free patients, but free hydrochloric acid was found in the duodenal contents of those with peptic ulcer. This was attributed to a disturbance in pyloric function, interfering with neutralization. Corresponding studies and comparisons were made by Berk, Rehfuss, and Thomas (1942).[57, 59] Although free acid was usually absent in the duodenal contents, they felt its presence was not abnormal. They observed that, in the normal subject, the duodenal bulb is endowed with a ca-

pacity to dilute, buffer, and neutralize gastric chyme that generally exceeds the physiologic needs, the average pH varying between 5.0 and 5.6, but in patients with duodenal ulcer this neutralizing ability is impaired, although not wholly lost. This particular subject has recently been reviewed by Comfort (1945),[93] who concluded that the reaction of the duodenal contents in the fasting normal individual is probably alkaline, although it becomes more acid each time the stomach empties, but the reaction of the duodenal contents in patients with duodenal ulcer is more acid both fasting and during digestive secretion.

Experimental Ulcer Production by Disturbance of Acid-Alkali Relationship.—

Administration of acid: In 1893, Matthes[332] resected segments of small bowel with the blood supply maintained, closed one end, and, bringing the open end out on the abdominal wall, was able consistently to produce necrosis and perforation by irrigation with a mixture of pepsin and hydrochloric acid. He studied the resistance of various tissues to digestion by gastric juice, and found that the gastric mucosa was most resistant of all, but his conclusion, as yet not invalidated, was that hydrochloric acid in sufficient concentration over a long enough period of time could produce necrosis of any tissue, and after necrosis occurred, enzymatic digestion of the tissue could proceed. Recently, Kolouch (1945)[277] has employed a similar method in studying the digestive effect of the constituents of gastric juice on various segments of bowel. Gallagher (1928)[170] produced gastritis, duodenitis, and acute ulcers in dogs to which he administered dilute HCl through a tube twice daily, but was unable to produce chronic ulcers. However, after about four weeks of instilling 0.4 per cent HCl through a gastric fistula for eight hours each day, Mann and Bollman (1932)[326] were able to produce chronic ulcers on the lesser curvature of the stomach. Friedenwald, Feldman, and Morrison (1933)[162] injected various substances into the muscularis of the dog's stomach; they found that weak solutions of hydrochloric acid had no effect, but stronger solutions produced definite ulceration. Acute shallow ulcers of the stomach and duodenum were produced by Ochsner, Gage, and Hosoi (1934, 1936)[167, 384] by feeding dogs 1 per cent HCl. In none of these experiments were the ulcers produced analogous to the typical peptic ulcers of man, although the experiments did demonstrate the corrosive action of hydrochloric acid. The importance of pepsin in conjunction with hydrochloric acid has been stressed by Matzner and Windwer (1937),[335] and by Schiffrin and Warren (1942),[441] who perfused the stomach and various segments of bowel with acid with or without pepsin. Ulcer production was at a maximum when pepsin was added to the solution. The optimum pH for acid-peptic digestion was found to be 1.1 to 1.5. The recent studies of Fogelmann's (1949)[158a] group indicate that the acidosis accompanying intragastric perfusion of acid-pepsin mixtures is important in the development of ulceration.

Deviation of duodenal contents: In 1909, Bickel[62] removed the duodenum in two dogs, transplanting the common bile and pancreatic ducts onto the abdominal wall and performing a gastrojejunostomy. One dog survived only 10 days; but the other dog, surviving 4½ weeks, developed two large and two small

ulcers in the neighborhood of the anastomosis, and, in addition, a large perforated ulcer in the jejunum 8 cm. distal to the anastomosis. Bickel felt that this was convincing demonstration of the importance of pancreatic, duodenal, and biliary secretions in the prevention of digestion of the intestine by acid chyme. Further proof was added by Baggio (1924),[28] who performed Roux en-Y gastrojejunostomies on dogs, either in conjunction with pyloric exclusion or resection of the pyloric portion of the stomach, so that the alkaline duodenal secretions entered the jejunum at a considerable distance from the gastrojejunal anastomosis. A substantial number of dogs surviving these procedures developed jejunal ulcers distal to the gastrojejunal anastomosis. Jejunal ulcers had previously been produced by Exalto (1911),[145] as a result of Roux en-Y gastrojejunostomies in conjunction with feeding hydrochloric acid. Another type of procedure, in which a pyloric exclusion was done, the duodenum severed at its distal end, the stomach anastomosed to the proximal jejunum, and the terminal end of the duodenum anastomosed to the cecum, was also done by Exalto. Each of three dogs developed a jejunal ulcer. Denk (1921)[109] was able to demonstrate two jejunal ulcers in a dog in which the pylorus had been resected, the jejunum divided 25 cm. from the pylorus, the aboral end being employed to make a gastrojejunostomy, and the oral end anastomosed to the terminal ileum so as to direct the duodenal contents to the terminal ileum. This procedure was supplemented by feeding the dog dilute hydrochloric acid.

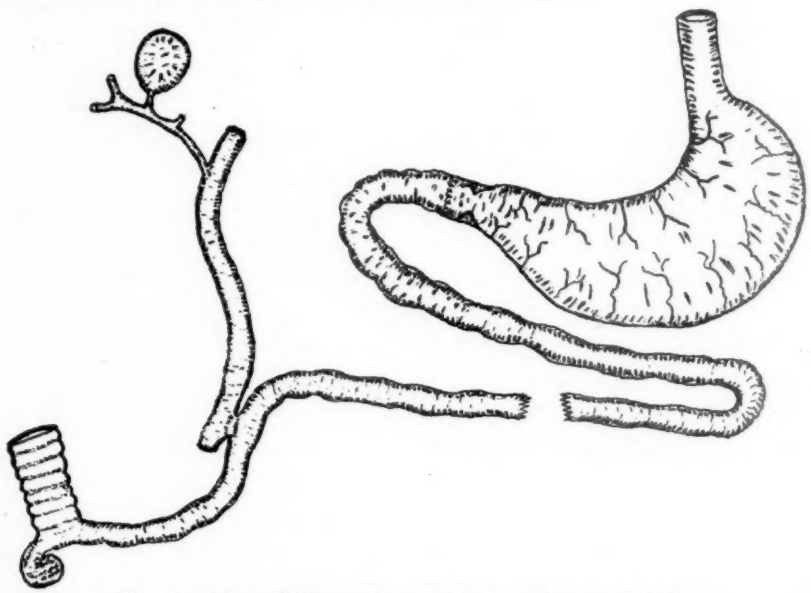


Fig. 3.—Mann-Williamson operation (diagrammatic).

The second experimental procedure of Exalto was slightly modified twelve years later by Mann and Williamson (1923),[329] who sectioned the duodenum just below the pylorus, did an end-to-end gastrojejunostomy, and anastomosed the distal end of the duodenum to the terminal ileum. Such an operation, which has come to be called the Mann-Williamson procedure in this country, will produce jejunal ulcers in 90 to 100 per cent of animals (Fig. 3).

This work has been confirmed abundantly by the work of Morton (1927),[370, 371] Weiss and Gurriaran (1929),[521] Weiss and Hubster (1931),[522] Owings and Smith (1932),[393] Orndorff, Fauley, and Ivy (1936),[391] and many others. These ulcers developed ten days to three months after the operative procedure,[322, 323] usually occurred just distal to the site of gastrojejunal anastomosis, were of the chronic variety, and were thought to be analogous to the peptic ulcers of human beings in every respect except as to location. Ivy (1946)[245] felt that they were entirely analogous to the postoperative jejunal ulcer occurring in human beings after gastroenterostomy or gastric resection.

In any case, such a procedure has proved to be of inestimable value in the experimental study of the pathogenesis and therapy of peptic ulcer. Owings and Smith (1932)[393] showed that if, when ulcers developed in Mann-Williamson dogs, the enteroenterostomy was taken down and the distal end of the duodenum anastomosed to the stomach, some of the ulcers would heal as a result of the return of the alkaline duodenal secretions. An increased acidity of gastric contents following the Mann-Williamson procedure has been shown by Wilhelmj and Finegan (1938),[525] who noted that the acidity continued to rise after a test meal, and the usual abrupt terminal decrease in acidity failed to occur. A marked increase in the intestinal phase of gastric secretion and in the continuous secretion after the Mann-Williamson operation was recorded by Ivy's group (1936),[391] who thought the ulceration was due to the deleterious action of such an unbuffered secretion on the especially susceptible jejunal mucosa. Recently, they have shown[185, 244] that the lowering of acid secretion by the administration of enterogastrone prevented ulcer formation in a sizable proportion of a series of Mann-Williamson dogs. In the hands of Saltzstein and his co-workers (1947),[433] however, enterogastrone prevented ulcer development in only 20 per cent of their Mann-Williamson dogs.

Various other experimental procedures have reproduced situations which, in effect, are analogous to a Meckel's diverticulum, in which secreting gastric mucosa is found adjacent to susceptible intestinal mucosa at a considerable distance from the alkaline secretions of the duodenum. Thus, Winkelbauer and Starlinger (1928)[531] produced jejunal ulcers in dogs by performing a pyloric exclusion operation, accompanied by gastrojejunostomy and an entero-enterostomy at a considerable distance from the gastrojejunostomy. Matthews and Dragstedt (1932)[334] anastomosed Pavlov gastric pouches to the terminal ileum, and produced ulcers in the ileum just distal to the anastomosis. The anastomosis of Pavlov or Heidenhain pouches to the jejunum was shown by Ochsner, Gage, and Hosoi (1934, 1936)[167, 384] to result in jejunal ulcer formation; these ulcers were prevented in a high percentage of dogs by directing the gall bladder bile to the gastric pouch.

Numerous attempts have been made to determine experimentally the relative importance in the protective process of dilution, neutralization, and buffering of the bile, pancreatic juice, and succus entericus.

The Role of the Succus Entericus in Neutralization: Comparatively little work has been done in evaluating the importance of the duodenal secretion

alone, as a neutralizing force protecting the intestine from the acid chyme. Grey (1919)[191] attempted a duodenectomy in dogs in three stages. After completion of the first two stages, which consisted of division of the common duct with cholecystojejunostomy, and transplantation of the major pancreatic duct to the jejunum with ligation of the accessory pancreatic duct, two of his dogs developed perforated jejunal ulcers. Another dog failed to survive the third stage (duodenectomy) and the only surviving dog died in 9½ months with intestinal obstruction from adhesions but no evidence of ulcer. This demonstrated that the duodenum was not essential for life. Shortly afterward, Mann and Kawamura (1922)[328] carried out similar procedures on a series of dogs and other animals, implanting the common bile and pancreatic ducts into the jejunum just distal to the gastrojejunal anastomosis. Two of ten dogs developed jejunal ulcers just distal to the suture line.

The Role of Bile in Neutralization: The importance of bile as a neutralizing and protective agent has received enough stress so that Bogoras (1925)[70] was led to advocate cholecystogastrostomy as a therapeutic measure for gastric ulcer; he reported that the free acidity of patients so treated declined after operation. More recently, Bergh (1938)[56] recommended the administration of bile salts as an adjuvant in the treatment of peptic ulcer; the x-ray evidence of ulcer healing noted in a large proportion of cases with this form of therapy was ascribed to a stimulation of the further flow of bile by the bile salts.

Various observers[129, 386] have noted that in experimental animals the pH of the liver bile is between 7.07 and 8.55, definitely on the alkaline side. However, the same observers recorded an acid pH for gall bladder bile, varying from 5.18 to 7.47. Neilson and Meyer (1921)[382] made similar observations in experimental animals, but in studies on a patient with a bile fistula, they found the pH to be 8.0, while gall bladder bile had a pH varying from 7.7 to 8.6. These observations should cast some doubt on the neutralizing power of the bile as delivered to the duodenum; nevertheless, a large amount of work has been done to demonstrate the importance of bile in protection against ulcer formation. Smith (1914),[457] as a result of his experiments, apparently believed that bile had a synergistic effect with hydrochloric acid in ulcer formation. However, Hooper and Whipple (1916)[231] found that deviation of the bile from the gastrointestinal tract, produced by ligation of the common duct with cholecystostomy, resulted in intestinal disorders, accompanied by melena, in all the dogs so treated, and one dog died with a large duodenal ulcer. At a later date, the same group (1935)[211] reported duodenal ulcers in 9 of 33 dogs prepared in this manner. Of 43 dogs in which the gall bladder had been implanted into the kidney pelvis with ligation of the common duct, Kapsinow (1926)[261] found duodenal ulcers in 17; these ulcers usually occurred in the neighborhood of the ampulla of Vater. Berg, Johnston, and Jobling (1927)[53] found duodenal or gastric ulcers in 7 of 9 dogs in which biliary fistula had been fashioned and (1930)[52] in 9 of 16 dogs with obstructive jaundice. Weiss and Hubster (1931)[522] were unable to produce ulcers in dogs by deviating the bile to the terminal ileum, but those dogs did develop an acute inflammation of the duodenum and antrum, which the authors thought to be a "pre-ulcer stage."

Obstructive jaundice produced by ligation and division of the common duct, as reported by Bollman and Mann (1932),[73] resulted in the development of acute, subacute, or chronic ulcers of the duodenum or stomach in 64 of 87 dogs. It is interesting to note that the development of ulceration could not be prevented by the oral administration of gall bladder bile twice daily. Ivy, Schrager, and Morgan (1932)[253] noted gastric or duodenal ulcers in 5 of 7 dogs with chronic icterus and hepatitis resulting from plastic procedures on the common duct. Duodenal ulcers were demonstrated by Blanck (1935)[65] in dogs with external biliary fistulas, but when such dogs were fed back the collected bile, they did not develop ulcers; Blanck's series of dogs was quite small, detracting somewhat from the significance of this work.

Using a fistula of the Mann type, McRoberts (1935)[346] studied the reaction of the duodenal content before and after the exclusion of bile from the duodenum by means of a biliary fistula; he found no significant alteration in the pH after bile was prevented from entering the intestine. Recently, by exposing the intestinal loops of dogs to various acid-pepsin mixtures, both with and without the addition of bile salts, Driver and Carmichael (1945)[126] found that the digestive action of the pepsin on the intestinal mucosa was markedly inhibited by the presence of bile salts at a pH of 1.25.

The Role of the Pancreatic Juice in Neutralization: Olch (1928),[387] as a result of his studies on regurgitation of duodenal contents in dogs, came to the conclusion that the most important factor in the reduction of gastric acidity was the pancreatic juice. The pancreatic ducts of dogs were ligated by Yesko (1928),[540] with only a slight resulting increase in the gastric acidity; Yesko made no mention of ulcer formation, but no protocols of individual dogs were included in his report. Elman and McCaughan (1927, 1928)[134, 139] ligated the minor pancreatic duct, established a pancreatic fistula via the major pancreatic duct, performed a cholecystostomy, and, by means of a series of tubes and clamps, established a system whereby, at will, they could either cause the exit of the entire external pancreatic secretion or cause the return of that secretion to the duodenum via the gall bladder and common duct. Dogs in which the pancreatic juice was withdrawn developed signs of gastric irritability, vomiting, and asthenia, and the gastric contents were found to contain a higher free and total acidity than normal, but when pancreatic secretion was then allowed to enter the duodenum, these dogs "came to life," and the acid values declined to normal. Elman and Hartmann (1931)[133, 137] showed that if these dogs were deprived of their external pancreatic secretion for two weeks or longer, even though they were kept in relatively good condition by the administration of intravenous fluids, the dogs developed duodenal ulcers just distal to the pylorus. However, Berg and Zucker (1932, 1934)[50, 54] recorded that of fourteen dogs maintained with a pancreatic fistula for fourteen to forty days, only one dog developed (duodenal) ulceration, and this dog showed evidence of obstructive jaundice. Moreover, five dogs with ligation of the pancreatic ducts showed no changes at all in their stomachs and duodenums. Berg felt the pancreatic juice was quite unimportant as a factor in protection of the mucosa from ulceration.

This problem has been studied rather thoroughly by Hoerner (1935)[220-224] in a series of experiments. Using a Mann type of fistula to the duodenum, he found that when the pancreatic ducts were "evulsed," the total buffer secretions in the duodenum diminished, but the remaining bile and succus entericus were capable of maintaining the normal reaction of the duodenal content, except just after the entrance of gastric juice of high acidity. Studying dogs with pancreatic fistulas, he found the duodenal content slightly more acid, and it is significant that 42 per cent of these animals developed peptic ulcer. The pancreatic secretion was always alkaline in reaction, but its buffering capacity was found to vary considerably, reaching a maximum one to three hours after the ingestion of food, and diminishing as the acidity of the duodenal content decreased. At its maximum buffering capacity, 1 c.c. of pancreatic secretion was capable of neutralizing an equal quantity of N/10 hydrochloric acid. It is peculiar that the dogs in which the pancreatic ducts were "evulsed" did not develop ulcer. Dragstedt (1943)[120] has also observed that, although nearly 100 per cent of dogs with pancreatic fistulas develop gastric or duodenal ulcer, and 33 per cent of dogs with ligated pancreatic ducts develop ulcer, in over 440 dogs in which the pancreas was removed entirely, gastric or duodenal ulcer was found "less than a dozen times." No adequate explanation for this phenomenon has as yet been advanced, and an experimental solution would contribute greatly to physiologic knowledge. Manhoff and Poth (1947)[319] recently found that ulcer formation and perforation occurred unusually rapidly with the administration of histamine-in-beeswax to dogs that had been pancreatectomized or in which the pancreatic ducts had been ligated.

An interesting clinical observation which to some extent corroborates this experimental evidence was cited by Morton and Graham (1930).[378] They recorded the case of a woman who had had a cholecystectomy and choledochostomy. After removal of the T tube from the common duct during the postoperative period, she became quite ill, vomited changed blood, and died. Autopsy showed a large stone, apparently missed at operation, obstructing the common duct, and another stone obstructing the pancreatic duct; the immediate cause of death was a large posterior wall duodenal ulcer which had eroded into the pancreas and caused the fatal hematemesis. There had been no evidence of this ulcer at the time of operation and it was felt that the ulcer formation was a result of interference with the discharge of alkaline bile and pancreatic juice into the duodenum.

Attempts to Assess the Relative Protective Value of Bile, Succus Entericus and Pancreatic Juice: The buffer value of bile and pancreatic juice has been compared in vitro by titration with hydrochloric acid by Jones (1931).[256] No great difference was found between the two, and he found that they were more or less compensatory, for when the buffer capacity of one decreased that of the other increased. It should be stated that Jones studied bile obtained from the common duct of an animal that had been cholecystectomized; it has already been noted that hepatic bile is much more alkaline than gall bladder bile.

Kehrer (1914)[264] was able to demonstrate three dogs with deep chronic ulcers, and three with acute erosions, out of fifteen dogs in which he had divided the common duct as well as the pancreatic ducts, anastomosing the gall bladder and major pancreatic duct to the ileum. This seemed to indicate that the duodenal juice had little protective value, but the experiments of Bauer and Aron (1933)[40] seemed to indicate that the duodenal juice was of prime importance. Unfortunately, these experiments were done only on one dog. This dog failed to develop ulceration after resection of the head and body of the pancreas, or even after division of the common duct and cholecystoileostomy at a second stage. However, following a third stage operation, in which the duodenum was resected and continuity re-established by a gastrojejunostomy, the dog died in nineteen days with three jejunal ulcers in the neighborhood of the anastomosis. Mann and Williamson (1923)[329] produced jejunal ulcers in only two of ten dogs in which the duodenum had been extirpated, with reimplantation of the pancreatic and bile ducts in the neighborhood of the gastrojejunal anastomosis, and in ten of thirty-one dogs in which the bile and pancreatic ducts were transplanted to the terminal ileum, but when all three types of secretion were deviated to the terminal ileum, nearly all the dogs developed jejunal ulcer.

The suggestion that bile was the most important of the three factors in neutralization was advanced by Owings and Smith (1932)[394] on the basis of their experiments. Of five dogs in which the common duct was divided and cholecystoenterostomy done eighteen inches below the ligament of Treitz, two developed duodenal ulcers, while these workers were unable to demonstrate ulcers following section of the pancreatic ducts and transplantation of the main pancreatic duct to the jejunum eighteen inches below the ligament of Treitz in another series of dogs. Strangely enough, when the procedure in this second series of dogs was supplemented by ligation of the common duct and cholecystoenterostomy (close to the site of anastomosis of the pancreatic duct), the dogs still failed to develop ulcer; this seems to indicate that the succus entericus is of some importance after all.

Graves (1935)[182] was unable consistently to produce ulcers either by the deviation of pancreatic juice or of bile to the terminal jejunum, but when he added to these procedures a modified Mann-Williamson operation, sectioning the jejunum above the site of transplant of the pancreatic or common bile duct, he found that ulcers developed near the anastomosis whether it was theoretically protected either by bile or pancreatic juice. However, he observed that the ulcers that occurred in the jejunum protected by pancreatic juice were not so large and not so often multiple as those occurring in the jejunum protected by bile, so he attributed more importance to the pancreatic juice.

A comparative study was made by DeBakey (1937)[107] in which, curiously, all his procedures were done in conjunction with pyloric occlusion and anterior (short loop) gastrojejunostomy, an operation which itself is known to favor the development of jejunal ulcer. With this procedure alone 10 (50 per cent) of 20 dogs developed jejunal ulcer; with deviation of the pancreatic juice to the terminal ileum added to this procedure 7 (70 per cent) of 10 dogs developed

jejunal ulcer; with deviation of bile to the terminal ileum accompanied by pyloric occlusion and gastrojejunostomy, 18 (90 per cent) of 20 dogs developed jejunal ulcer; and in a series of 10 dogs in which all these procedures were done, all of the dogs developed jejunal ulcer. Thus, he concluded that bile was the most important, pancreatic juice less important, and the succus entericus the least important as a means of neutralizing the gastric acid and preventing ulcer formation.

Bachrach, Schmidt, and Beazell (1939)[27] attached some importance to the bile. In a series of 19 dogs with the pancreas separated from the duodenum, only 1 dog developed a duodenal ulcer. Perforated duodenal ulcers developed in 2 dogs with biliary fistulas in which the bile was fed back through a long tube passing through the common duct into the bowel and terminating 50 cm. below the ampulla of Vater, but 13 other dogs in which the bile was returned into the duodenum failed to develop ulcer.

Total Intragastric Regurgitation of Alkaline Duodenal Contents.—With such a weight of evidence, albeit somewhat conflicting evidence, that the succus entericus, bile and pancreatic juice are important in protecting the gastric and duodenal mucosa from the digestive action of the gastric juice, it would seem reasonable to suppose that by emptying some or all of these secretions directly into the stomach, the gastric acidity might be reduced sufficiently to ablate the ulcer diathesis. Schmilinsky (1918)[443] advocated as a mode of surgical therapy for ulcer a procedure which had been tried in dogs by Chlumsky[88] in 1900. This consisted essentially of a von Eiselsberg pyloric occlusion, combined with sectioning the proximal jejunum, the oral end of which was anastomosed to the fundus of the stomach, while the aboral end was anastomosed to the stomach in the region of the antrum. Although he noted that the gastric acid values were quite high during digestion after this procedure, Schmilinsky reported cures in five patients with duodenal ulcers and three patients with jejunal ulcer.

The effects of deviation of the pancreatic juice or bile into the stomachs of dogs on the acidity of gastric secretion were studied by Grey (1916, 1917).[189, 190] He reported that cholecystogastrostomy had no appreciable effect on the acidity of the gastric contents, but that the presence of pancreatic juice in the stomach, as shown by trypsin determinations, actually led to a moderate increase in acidity in the late phase of the digestive process, which was attributed to compensatory activity of the gastric glands. It has since been shown[26] that alkali is an effective stimulus of gastric secretion.

Schmilinsky's procedure was repeated in dogs by Keppich (1921)[269] with the resultant development of jejunal ulcers, but when a resection of the pyloric antrum or a hemigastrectomy was added to this procedure, no ulcer developed. The same procedure, with the variant of making an end-to-end anastomosis between the pyloric end of the stomach and the aboral end of the jejunum, was repeated by McCann (1929),[339] who reported that 80 per cent of his dogs developed jejunal ulcers. He found the essential character of the acid secretory curve unchanged after such an operation, but the acidity rose at the time of ulcer development. McCann's procedure, in turn, was repeated by Weiss and

his associates (1932),[520] although modified by using a short duodenal loop anastomosed to the antrum instead of to the fundus. By thus making the duodenal contents immediately available for protection of the jejunal mucosa, they were able to prevent the development of jejunal ulcer in all fourteen of their dogs. The importance of neutralization at the stoma was also emphasized by the work of Maier and Grossman (1935),[318] who felt that in the Schmilinsky procedure and its variants some of the alkaline duodenal content is lost for effective neutralization at the stoma, and the procedure is therefore less valuable than an ordinary gastrojejunostomy.

Wangensteen (1940, 1942)[505, 512] gave the Schmilinsky procedure a clinical trial in three cases of gastrojejunal ulcer. One of these patients died with a perforated new marginal ulcer, the second died with a gross hemorrhage from a gastric ulcer, and the third did not show much decrease in acidity of secretion and maintained a prolonged emptying time. The experimental evidence at hand indicates that there is no rational basis for the clinical use of such an operation.

Ulcer Production By Histamine.—The known property of histamine to evoke a highly acid gastric secretion has stimulated numerous attempts to produce ulcers experimentally by histamine injection. Buchner and Molloy (1927)[80] and Burkle-de-la-Camp (1929)[82] were able to produce acute but not chronic ulcers in the forestomach of rats by repeated subcutaneous injections of histamine. In the hands of O'Shaugnessy (1931)[392] this method failed with cats, but hemorrhagic areas and acute ulcers were produced by injecting histamine directly into the muscularis of the stomach of these animals. Chronic ulcers were finally produced in the forestomachs of rats, although not consistently, by Harde (1932)[203] by repeated subcutaneous administration of histamine. Flood and Howes (1934)[156] found that artificial defects created in the mucosa of the stomachs of cats and dogs healed completely in two weeks, but when histamine was administered parenterally twice daily to these animals the healing process was considerably delayed. Extension of artificially produced mucosal defects with histamine administration was noted by McIllroy (1927).[344] Orndorff, Bergh, and Ivy (1935)[390] attempted to maintain a hypersecretion in dogs by injecting every two hours either histamine (producing a juice rich in acid), pilocarpine (producing a juice rich in pepsin), or a combination of these drugs, but they were unable to produce ulcers in these dogs.

It remained for Walpole, Varco, Code, Hay, and Wangensteen (1940-1942)[92, 212, 490, 494] to determine a suitable vehicle (beeswax and mineral oil) for the histamine, so that by a single injection each day, a hypersecretion could be maintained over a twenty-four hour period. The prolonged action of this acid gastric juice resulted consistently in the development of subacute or chronic, frequently perforating ulcers in the stomachs and duodenums of dogs, guinea pigs, cats, chickens, ducks, woodchucks, calves, monkeys, rabbits, and swine. Ulcer production in the latter animal is of especial interest, since the stomach of the pig is more like that of man than the stomach of any other animal. Curiously enough administration of an antihistamine substance, Benadryl, in conjunction with the histamine-in-beeswax, failed to alter the gastric secretory

response or to prevent the formation of ulcers,[165] and the administration of enterogastrone likewise failed to prevent the formation of histamine-induced ulcers.[198]

The acid-peptic factor in ulcer production and the relative protective value of various neutralizing secretions have been discussed in considerable detail because of the importance of this factor in connection with ulcer surgery. It is, however, obvious that this is not the only factor concerned in the causation of peptic ulcer. More than forty years ago, MacCallum (1904)[314] wrote: "It may be said that gastric ulcers may be produced by anything which causes necrosis of the mucosa of the stomach, and thus subjects it to the digestive action of gastric juice." This observation, to a greater or lesser extent, still holds good today. A number of other factors concerned in the etiology of peptic ulcer will be discussed more briefly.

The Mechanical (Traumatic) Factor

The observation of Aschoff (1924)[20] that the lesser curvature of the stomach, or "Magenstresse," has a different anatomic arrangement than the rest of the stomach has led many workers in this field to theorize that, in the lesser curvature region, the pyloric antrum, and the first portion of the duodenum, the regions where benign ulcers most commonly occur, since the mucosa is more fixed and smoother than elsewhere, and its blood supply is less rich, it has less mechanical protective value, and consequently is more subject to the traumatic effect of ingested materials. Halperin (1926)[202] was one of the first in this country to subscribe to this theory. However, the healing time of acute ulcers produced by the submucosal injection of silver nitrate was not affected by massaging the region with bread crumbs until congestion occurred, according to Ivy (1920).[240] Gallagher (1927)[168] found the gastric mucosa of dogs quite resistant to trauma produced by the application of clamps. Baggio (1927)[29] was able to produce lesions of the gastric mucosa by infolding the anterior gastric wall with sutures, producing partial obstruction; erosions and ulcers occurred in the infolded portion of the mucosa, and, directly opposite, in the areas where ingested material impinged on the mucosa.

This theory was emphasized in conjunction with the acid-peptic factor by the Mayo clinic group as a result of their observations on Mann-Williamson dogs. Mann[322, 323, 324] called attention to the fact that ulcers in these dogs could not be due to the operative trauma, because they developed after the suture line had healed. He observed particularly that the ulcers occured at the same site, just distal to the suture line in the jejunum and often opposite the stoma, and attributed this to the "jet" effect of material squirted through the pylorus by peristaltic waves. Moreover, the lesions developed more rapidly if the stoma were small than with a large stoma. Morton (1927)[372] noted that when Mann-Williamson dogs that had already developed jejunal ulcers were reoperated upon, performing an anterior gastroenterostomy, the original jejunal ulcers healed, but other jejunal ulcers developed where the new "jet" of chyme impinged on the jejunal mucosa. The importance of the lesser curvature as an area susceptible to trauma was also emphasized by Morton (1927, 1928).[370, 373, 374]

Mucosal defects produced by snipping out areas of mucosa took longer to heal on the lesser curvature and in the antral region than in other areas, and when such defects were produced in conjunction with the Mann-Williamson procedure, only those defects on the lesser curvature became chronic ulcers. Likewise, when patches of jejunum were implanted in the stomach of dogs then subjected to the Mann-Williamson procedure, only those patches in the lesser curvature region exhibited ulcers. Concerning two of the ulcers in McCann's (1929)[339] dogs, which had a modified Schmilinsky procedure performed, numerous dog hairs were found embedded in the base of one, and the other, which was perforated, had a piece of turnip protruding through it. The force required to embed these objects was attributed to the "jet effect."

Jenkins and Palmer (1931)[255] attempted to eliminate the mechanical factor by varying the Mann-Williamson procedure, making an unusually wide stoma side-to-side gastroenterostomy instead of the usual end-to-end anastomosis, but were unable to show any difference in the incidence of ulcer in their dogs. The consistency of the diet as a traumatic factor was emphasized by the work of Fauley and Ivy (1930).[147] Defects in the gastric mucosa, produced by excising small portions, healed irrespective of the diet administered, but if nonabsorbable material was sutured in the base of the defect, chronic ulcers developed if the dogs were fed a rough diet, while the defects healed if a bland diet was administered. Driver, Chappell, and Carmichael (1945)[128] furnished further proof of the importance of Mann's "jet effect." Exposing loops of dogs' intestines to 0.1 per cent pepsin in N/10 HCl under various hydrostatic pressures, they found that a rise in intraintestinal pressure resulted in a marked increase in the extent of peptic digestion, leading to perforation in a shorter time; in controls exposed to saline alone under the same pressures no necrosis occurred.

Diminished Tissue Resistance to Acid-Peptic Digestion

The Vascular Factor.—For many years pathologists have observed that sclerosis or thrombosis of small arteries is frequently seen in resected or autopsy specimens of peptic ulcer. This has led some to believe that ulcer formation is in part due to localized areas of anemia, actual necrosis from loss of blood supply, or some type of embolic phenomenon. Indeed, ulcers have been produced experimentally in the stomach of the rat[51] by vascular ligation, but it has already been noted that the stomachs of man and dogs have a different anatomic arrangement of the blood supply, and, in fact, obliteration of the greater portion of the blood supply in the dog's stomach results in no great change in the mucosa.[297] Baronofsky and Wangensteen (1945),[37] however, have been able to produce gastric and duodenal ulcers, many of which perforated, in various types of experimental animals, by provoking chronic arterial spasm through the parenteral administration (in beeswax) of such vasospastic substances as Pitressin and epinephrine.

The Minnesota group also became interested in the fact that peptic ulcer or hematemesis occasionally occurred as a complication of fractures[511] and were able to demonstrate in a variety of animals that fracture of the long bones, curettement of the bone marrow,[355] or actual intravenous injection of normal

human breast fat[36] resulted in the development of gastric or duodenal ulcers in a rather low percentage of animals. Since it was demonstrated[356] that fractures in man, or fractures or curettement of the bone marrow in dogs failed to cause any stimulus of gastric secretion, it was concluded that the ulcers obtained were on the basis of fat emboli, which they thought produced localized areas of anemia more susceptible to the digestive activity of the gastric juice.

Considerable interest has been shown by clinicians for many years in the relationship of caffeine-containing drugs to ulcer development. Caffeine and caffeine-containing beverages have been shown to stimulate gastric secretion in man and the cat but not in the dog.[353, 426, 427] Gastric ulcers or erosions have been produced in cats[425] and guinea pigs[258] by the administration of caffeine-in-beeswax. The mechanism by which these ulcers are produced has been studied rather thoroughly on a histologic basis by Roth and Ivy (1945).[424] They found that with the prolonged administration of caffeine, a vasodilatation and vascular engorgement and stasis developed in the gastric wall; these were thought to result in local anoxia and increased capillary permeability, resulting in an ideal site for the initiation of digestion by the highly acid gastric juice. Baronofsky (1945)[34] has shown that the vascular stasis produced by splenic vein obstruction abets the ulcer diathesis.

The Allergic Factor.—Shapiro and Ivy (1926)[450] produced acute gastric ulcers in previously sensitized or passively immunized dogs or rabbits by injection in the submucosa of various antigens, such as beef, protein, albumin, etc. They felt that a similar phenomenon might occur in man as a result of sensitization to some type of protein to which he is repeatedly exposed, the process then being enhanced by the trauma of ingested food and acid-peptic digestion. Recently, Wangensteen's (1948)[166] group have sensitized dogs in a somewhat similar manner, and observing the gastric and duodenal mucosa in the sensitized animals during the intravenous injection of the antigen concerned, found that a marked edema developed. With repeated administration of antigen, three of six sensitized dogs developed ulcers, and when histamine-in-beeswax was given daily to another group of sensitized dogs, the rapidity of ulcer development was markedly increased over that normally expected.

The Nutritional Factor.—The nutritional status of the body as a whole appears to be an important factor in determining mucosal resistance to acid-peptic digestion. According to Bollman and Mann (1927)[72] in animals with an Eck fistula, resulting in disturbances of protein metabolism, there is a high incidence of chronic duodenal ulcer. Although guinea pigs rarely develop spontaneous peptic ulcers, Smith and McConkey (1933)[458] found that 26 per cent of their guinea pigs maintained on a diet deficient in vitamin C developed chronic ulcers similar in location and appearance to those seen in man.

It was felt by Weiss and Aron (1933)[519] that the ulcers resulting from Mann and Williamson's procedure might be due to digestive disturbances, especially with regard to protein metabolism, cachexia, anemia, and atrophy of the gastric mucosa; when histidine and tryptophane or histidine alone were given daily to their Mann-Williamson dogs, they failed to develop ulceration as late

as ten weeks after operation. Moreover, Fauley and Ivy (1936)[148] found that a special easily assimilable diet would delay the appearance of ulcer in Mann-Williamson dogs, but if such dogs survived more than seventeen weeks, nearly all the dogs developed ulcer. Nutritional changes in Mann-Williamson dogs, and especially a fall in serum proteins, were noted by Flood and Mullins (1936),[157] but six of eleven of their dogs which were given histidine daily developed jejunal ulcer. Likewise, Wu (1937)[539] was able to demonstrate jejunal ulcers in four of six Mann-Williamson dogs to which histidine was administered daily, and Sandweiss' group (1937)[437] demonstrated ulcers in all their histidine-treated dogs which survived the Mann-Williamson procedure more than three days.

The studies of Weech and Paige (1937)[516] give further indication of the importance of protein metabolism in relation to ulcer development. Of twenty-two dogs feed on a diet deficient in protein for an average period of ninety days, eight developed ulcers of the stomach or duodenum and another five showed gastric or duodenal erosions. Li and Freeman (1946)[303] demonstrated an even higher incidence of gastroduodenal ulceration in dogs on a protein deficient diet; twelve weeks appeared to be the minimum time of such a diet necessary to produce ulceration. The development of perforated duodenal or jejunal ulcers after pylorectomy in hypoproteinemic dogs has been shown by Mecray, Barden, and Ravdin (1937).[348] Thus it appears that the state of nutrition, particularly with regard to protein metabolism, is of great importance in ulcer development; however, the findings of Weiss and Aron that histidine is the single important essential amino acid concerned have not been substantiated. These considerations have resulted in the recent popularity of various regimes, such as that of Ruggiero's group,[428a] for the treatment of peptic ulcer by the administration of protein hydrolysates.

The Inflammatory Factor.—The inflammatory basis of ulcer development was strongly urged by Konjetzny (1931),[283] on the basis of pathologic studies. Since gastric juice will not ordinarily digest normal gastric or duodenal mucosa, he felt that peptic ulcers developed in a damaged mucosa as a result of gastritis or duodenitis, and never developed in a normal gastroduodenal mucosa.

Several attempts have been made to show that peptic ulcer is an infectious disease, the result of invasion of a specific organism. Turck (1906)[483] produced ulcers of the stomach and duodenum by feeding dogs certain strains of *Bacillus coli,* but was unable to prevent the healing of artificially produced gastric mucosal defects by the intravenous injection of colon bacilli obtained from feces of patients with peptic ulcer. The theory of "elective localization of streptococci" was propounded by Rosenow (1913, 1916).[422, 423] Certain strains of streptococcus (viridans and hemolyticus) were isolated from the ulcers of clinical patients at the time of operation, and intravenous injections of these organisms produced gastric or duodenal ulcers in various experimental animals. These results were confirmed by Hardt (1916).[204] Moreover, organisms obtained from such experimentally produced ulcers, when injected intravenously in another experimental animal, would again cause ulcer formation. The clinical im-

portance of foci of infection, harboring these organisms, in the tonsils, teeth, gall bladder, and appendix, was stressed by Rosenow. Hoffmann (1925)[223] isolated a gram-negative rod from the gastric contents of ulcer patients, and felt that it represented a specific organism, since intra-abdominal or intramuscular injection in guinea pigs was followed by the development of gastritis, duodenitis, or ulcer, and these lesions could be reproduced after passage through several animals. As a result of immunologic studies with organisms isolated from ulcers in clinical patients, and the serum from those patients, Saunders (1930)[439] thought that a nonhemolytic streptococcus of the alpha type was the specific organism involved.

The multiplicity of organisms to which ulcer causation has been attributed seems to cast a shadow of a doubt on any specific bacterial theory and to suggest that such organisms may have been secondary invaders. In addition, there is some evidence in opposition to such theories. Hardt (1916)[204] was unable to produce ulcers in rabbits by the intravenous injection of *B. coli*. Wilensky and Geist (1916)[524] were unable to influence the healing time of artificially produced mucosal defects in the stomach of cats, despite repeated injections of various strains of streptococci cultivated from human ulcers. Ivy (1920),[240] producing ulcers by silver nitrate injection in the gastric mucosa, was unable to alter the healing time of these ulcers by massaging them with various strains of streptococci (viridans, hemolyticus) and staphylococci. He was also unable[241] to produce ulcers by injections of streptococci in the gastroepiploic vessels, or by feeding streptococci to healthy dogs. It is interesting that two dogs with distemper, who had achlorhydria, developed duodenal ulcers. Ivy thought that the relatively high acidity occurring in the normal stomach was incompatible with the life of most bacteria and that the production of ulcers by "specific bacteria" was attributable to nutritional disturbances or foreign protein reactions.

The Neurogenic Factor

The frequent appearance of peptic ulcer in emotionally overactive, driving, or aggressive individuals, or in those whose occupation of necessity subjects them to a life of high tension such as, for example, physicians and taxicab drivers, has led many clinicians to suppose that a neurogenic factor is involved in ulcer genesis. This has resulted in various types of clinical application. Crile (1931, 1933)[100, 101] felt that in such "hyperkinetic" individuals there was a tremendous overactivity of the sympathetic nervous system resulting in pylorospasm (and retained gastric secretion). On the basis of this theory, he advocated (and practiced) suprarenal denervation for uncomplicated peptic ulcer, but this mode of therapy never gained any great popularity. The reintroduction by Dragstedt (1942)[119] of vagus resection as a surgical procedure useful in treating peptic ulcer is based on his observation that the ulcer patient has an excessive continuous secretion of acid gastric juice, which is particularly deleterious at night, when unneutralized by food. This secretion is said to be mediated through the vagus nerves by psychic stimuli. The work of Wolf and Wolff (1943),[534] showing the relationship of emotional activity to gastric secretion, has stimulated the interest of psychiatrists and psychosomat-

icists in the disease. Recent studies by Boerema (1948)[69] of the increased incidence of ulcer in Holland during the World War II concluded that ulcers occurred on the basis of neurogenic spasms of the gastric and duodenal musculature, resulting in localized areas of anemia.

The spontaneous occurrence of acute perforating gastric or duodenal ulcers in three patients who had been operated on for cerebellar tumors led Cushing[102] to suggest a definite relationship between ulcer causation and the midbrain. Keller, Hare, and D'Amour[265] were able to produce hemorrhagic erosions in animals with experimental lesions of the brain stem.

The effects of vagus resection and the relationship of the vagus nerves to gastric secretion are discussed in more detail elsewhere. It is interesting to note, however, that experimentally, gastric ulcers have been produced in rabbits as a result of bilateral vagotomy.[10, 46, 389] However, vagotomy in dogs has failed to produce ulcerative lesions,[46] and chronic stimulation of one vagus nerve in the dog has not resulted in ulcer formation.[61] Beaver and Mann (1931)[47] minimized the importance of nerve impulses in ulcer development by showing that neither bilateral vagotomy nor resection of the splanchnic nerves would prevent the development of jejunal ulcer in a Mann-Williamson dog. However, the administration of a cholinergic drug, pilocarpine, by various parenteral routes has resulted in the development of acute ulcers in rabbits.[163, 304, 535] These lesions were attributed by Underhill and Freiheit (1928)[484] to localized areas of anemia as a result of the excessive increase in gastric motility. Experimental ulcers have also been produced by interference with the sympathetic nervous system in various ways: by bilateral adrenalectomy,[320, 321] section of the splanchnics,[10, 130] and removal of the prevertebral (celiac, superior, and inferior mesenteric) ganglia.[311] It should be stated that many of these experimentally produced ulcers were not at all like those seen in man.

Years ago, Alvarez (1932),[8] after reviewing the experimental work-up to that time, listed five ways in which he thought nervous influences might act to produce peptic ulcer, and it seems that these are still applicable. These mechanisms were:

1. An increase in acidity and peptic activity of the gastric juice (actually a result of an excessive volume of secretion)
2. A diminution in the amount of mucus secreted
3. An ischemia of the tissues produced by spasm of the blood vessels or of the muscle of the stomach
4. The possibility of pancreatic and biliary secretions "drying up" as does the saliva under emotional stress
5. Stagnation of gastric contents, with increased acidity, as the result of pylorospasm

Miscellaneous

Peptic ulcers are known to occur as an occasional complication of severe burns. Harkins (1938)[205] reviewed the literature on the subject of these "Curling's ulcers," and thought that a septic cause was the most likely, since they most frequently occur in association with large sloughing infected burns. Others have attributed the occurrence of these ulcers to protein deficiency.

Gastric and duodenal ulcers have been produced experimentally by numerous other methods, none of which seem closely related to the process of development of ulcer in man. These methods include exposure of the gastric mucosa to roentgen rays,[535] administration of toxins such as cinchophen,[461, 486] and administration of posterior pituitary extract.[114, 358]

Thus, in summation, it may be said that on the basis of the evidence at hand, the acid-peptic factor appears to be the most important in the etiology of peptic ulcer, but the mechanical factor and the neurogenic factor may play an important role, and the resistance of the tissues to digestion, as determined by a variety of factors, is of great consequence. It must not be forgotten that the acid-peptic factor cannot be entirely separated from the neurogenic factor, and that all the aforementioned factors are interrelated.

OPERATIONS FOR PEPTIC ULCER

Indications for Operation

It is not within the scope of this work to enter into any extended discussion with regard to indications for operation for ulcer. In general, there is a fairly close agreement, among both internists and surgeons, concerning these indications. All are in agreement that a diagnosis of perforation merits an immediate emergency operation; usually a simple closure of the perforation, either by suture or by an omental graft[33, 181] is the procedure of choice, although resection has been occasionally recommended.

There is rather general agreement that operation is necessary for gastric ulcers which do not heal promptly,[4] because of the possibility of the presence of early carcinoma; for ulcers which cause cicatricial obstruction to the gastric outlet; for ulcers, including postoperative gastrojejunal ulcers, which do not respond to an adequate trial of medical therapy; and for ulcers which have been the cause of repeated episodes of hemorrhage.[3, 67, 341, 347] Only in the matter of surgery in relation to an actively bleeding ulcer is there a wide diversity of opinion, which ranges from the idea of medical treatment for all, with immediate feeding, as advocated by Muelengracht (1939)[359] and Andresen (1939),[12] to the extreme of advising early operation for all severely bleeding ulcers, as does Finsterer (1939).[154] The length of time the patient has been bleeding, the severity of the hemorrhage, and the age of the patient, as emphasized by Blackford (1939),[64] are important considerations here, and the majority of surgeons, such as Hinton (1938)[219] and Wangensteen (1940),[502] choose a middle ground between these two extremes.

Variety of Operations for Ulcer

When surgery has been decided upon for the ulcer patient, the surgeon has at his disposal a great variety of procedures from which to choose the one which will benefit his patient to the greatest degree. Many of these have proved to be hopelessly inadequate and do not merit discussion; others by their inadequacy have proved educational particularly with regard to the pathologic physiology of the upper gastrointestinal tract. None of the operations in use today gives 100 per cent perfect results, but surgeons and experimentalists are

constantly striving toward such a goal, and for that reason a number of procedures will be discussed briefly, the emphasis being placed on gastric resection and its variants.

Vagus Resection.—Bilateral resection of the vagus nerves as advocated by Latarjet, and as recently reintroduced and popularized by Dragstedt (1943-1946),[122, 123, 124, 478] Moore (1946-1947),[366, 368] Grimson (1946-1947),[193, 428] and their colleagues is a procedure which must still be considered in the experimental stage. When one considers the experience the surgical profession has had with gastroenterostomy, one can agree with Small (1947),[456] who, in his thorough review of the subject, stated that a good many years will have to pass before such an operation is adequately evaluated. Meanwhile, in the period of evaluation, it seems reasonable to state that if this procedure is complicated by a variety of other procedures done in conjunction with it, no long-term evaluation of the pure operation will be possible. Moreover, since the presence or absence of carcinoma in a gastric ulcer can be determined with certainty only under the microscope,[4] it seems fair to state that vagus resection should never be used alone as definitive treatment for gastric ulcer. Also, since vagus resection results in considerable gastric atony and marked prolongation of the gastric emptying time,[99, 350, 428, 478] it should not be used alone as definitive therapy for ulcers already causing obstruction. One cannot help wondering like Warren (1947),[513] if the obstructive effect of vagotomy may not interfere with the neutralization of gastric acid by the duodenal juices, and if the neutralization process may not be further diminished by a decreased secretion of gastric mucus.

The most striking early result of vagus resection is an immediate cessation of ulcer pain in almost all cases,[124, 368, 428] as well as a healing of the ulcer as manifested by x-ray examination in a relatively short period of time in the majority of cases. The volume of gastric secretion is diminished particularly with regard to that secretion occasioned by central stimuli,[478] and the volume and acidity of juice secreted in response to alcohol is diminished,[99] but the secretory response to histamine remains the same. Theoretically, the operation must consist of a complete section of all vagus fibers, since it has been shown[161] that unilateral vagus section has no effect on gastric secretion, although Walters (1947)[499] and Ruffin (1948)[427a] pointed out that excellent clinical results have been obtained in patients who have had incomplete vagal section as indicated by the insulin test. The most troublesome ensuing complication is a decreased gastric motility, with stagnation of gastric contents, annoying sensations of fullness, and frequent regurgitation of ingested material, which may be so severe as to require pyloroplasty, gastroenterostomy, or gastric resection. Diarrhea and cardiospasm may also occur.

The early enthusiasm for this operation of Dragstedt (1945),[120a, 124] who reported cures in 35 to 39 patients, and who later reported (1947)[121a] 160 vagotomies (some associated with gastroenterostomy) during a four-year period with only 5 (3 per cent) showing even suggestive evidence of recurrence, must be tempered with the knowledge that an increasing number of poor results are being reported from this operation. While the mortality rate is generally considered

to be almost 0,[366] and Dragstedt[121a] reported no deaths in 150 cases, the Mayo Clinic group (1947)[499] reported 4 deaths, 1 from a perforation of a duodenal ulcer, in a series of 84 vagus resections, a mortality rate of almost 6 per cent, which is higher than the mortality rate for gastric resection in the most experienced hands. Weeks, Ryan, and Van Hoy (1946)[517] reported 2 deaths, 1 due to perforated duodenal ulcer, the other due to cardiac arrest on the operating table when traction was exerted on the vagus nerve. Moore (1947)[366] considered that only 87 per cent of the results in a series of 74 vagus resections could be regarded as good; 5 patients (6.7 per cent) had either symptoms of recurrent ulcer or actual demonstration of such a recurrence, 2 others had bleeding presumably of ulcer origin, about two weeks postoperatively, and 5 others had annoying symptoms sufficiently severe to detract from the results. Of 84 cases reported by Walters' group (1947),[499] the ulcer failed to heal in 7 (8.3 per cent). Warren (1947)[513] reported that in a series of 15 vagotomies, 1 patient developed a new ulcer, and 2 others had retention severe enough to require further surgery.

Furthermore, caution with regard to vagus resection should also be engendered by a survey of certain experimental work. As recorded previously, although Hartzell (1929)[209] reported a reduction in gastric acidity after bilateral vagus section in dogs, Vanzant (1931),[487] working with the same dogs 2½ years later, found their secretion approximately normal. Shapiro and Berg (1934)[449] presented evidence that after vagus section the stomach achieved some degree of autonomous control of acid secretion, this control perhaps being localized in the plexuses of Meissner and Auerbach. It has been shown by Beaver and Mann (1931),[45] Oliver (1947),[388] and Saltzstein's group (1947)[434] that vagotomy fails to prevent the appearance of jejunal ulcers after the Mann-Williamson procedure in dogs. Only Harkins and Hooker (1948)[206] reported that such ulcers were prevented by vagotomy. They, as well as Lillehei (1947),[305] found that vagotomy in dogs did not prevent the production of ulcers by histamine-in-beeswax, although Lillehei noted that the appearance of the ulcers was slightly delayed.

Without being unduly pessimistic, therefore, it should be stated that the operation of vagus resection merits considerable further evaluation, and should be employed with considerable caution in selected cases, and not as a routine procedure.

Pyloroplasty.—For many years, pyloroplasty of various types including gastroduodenostomy, with excision of the ulcer, was advocated, particularly by the Mayo Clinic group (1930)[259] and Finney (1929).[153] Such procedures have some experimental basis in the work of Elman's group (1931, 1933),[136, 140] Morton (1934),[376] and others previously reported. However, they are applicable only in certain situations and more specifically are of no value in dealing with those ulcers frequently found on the posterior wall of the duodenum, eroding into the pancreas. In addition, the results of such procedures have proved grossly unsatisfactory in the hands of many.[232, 290, 485] Hence, no attempt will be made to compare such procedures with more thorough and perhaps more statistically justifiable operations.

Gastroenterostomy.—Gastroenterostomy was introduced by Wölfler in 1881, and during the next forty to fifty years a great deal of hope was maintained for this operation as a curative procedure for peptic ulcer. During the second and third decades of the twentieth century, this procedure was gradually abandoned in favor of a more radical resection by European surgeons, but American surgeons were much more tenacious in their opinion that posterior gastrojejunostomy was a satisfactory operation. As cases were followed longer and longer, the *bête noire* of jejunal or marginal ulcer appeared more and more frequently, substituting a more undesirable condition for the original ulcer. Some of the earlier figures for the incidence of jejunal ulcer after gastroenterostomy may reflect an inadequate follow-up period and poor methods of analysis of results, or might be colored by the aversion of a group of surgeons to the more radical operation. In 1910, W. J. Mayo[336] reported only 3 jejunal ulcers in 1,141 gastroenterostomies. Judd[257] in 1921 reported an incidence of 1.2 per cent jejunal ulcer in 4,324 gastroenterostomies done at the Mayo Clinic. Balfour[31] reported an incidence of 1.6 per cent jejunal ulcer for the same institution in 1926, but this figure was obtained by the fallacious method of comparing the number of gastroenterostomies done during the period concerned, with the number of gastrojejunal ulcers operated on. This group felt that gastroenterostomy yielded approximately 90 per cent good results. Likewise, Moynihan[379] in 1928 reported an incidence of only 4 per cent jejunal ulcer with his gastroenterostomies. An incidence of 1.7 per cent jejunal ulcer after gastroenterostomy was reported in 1925 by Walton,[500] but nine years later his figure had risen[501] to 3.4 per cent.

As the years advanced, it became more apparent that such figures were a false picture of the true value of this operation. DeTakats (1926)[110, 111] reporting on the experience of the University of Budapest, as early as 1926, gave an incidence of 18 per cent jejunal ulcers after gastroenterostomy, and felt that only 50 per cent of the patients so treated could be classified as excellent results. When a von Eiselsberg pyloric occlusion was combined with a gastrojejunostomy, this figure reached 21 per cent. Haberer (1921)[201] reported fourteen jejunal ulcers in seventy-one patients who had the von Eiselsberg procedure. Lewisohn (1925),[300] in this country, startled more complacent surgeons by recording an incidence of 34 per cent gastrojejunal ulcer after gastroenterostomy, both with and without pyloric exclusion. Other more recent figures illustrating the increasing occurrence of jejunal ulcer after gastroenterostomy as the follow-up period increased are: 24 per cent reported by Strauss' group (1928);[472] 48.3 per cent (including those suspected clinically) reported by Newburger (1937),[383] who noted that every case in which a patient under 30 years of age had a gastroenterostomy proved to be a failure; 12.3 per cent reported by Graham (1938);[179] 16.4 per cent reported by Hinton (1935),[218] and, five years later, dealing with material from the same clinic, 24.4 per cent reported by Church and Hinton (1940).[89] Wright (1935)[537] reported the results of a collective inquiry by the Fellows of the British Association of Surgeons, indicating that in 2907 gastroenterostomies, there had been 220 proved and suspected jejunal ulcers, an incidence of 7.5 per cent. The experience of Hurst and Stewart (1928)[236] is par-

ticularly interesting. They found, in routine autopsies on 131 cases with gastrojejunostomy done at some previous time, that 25 (19%) of these cases had gastrojejunal ulcers, and of the 42 cases autopsied more than 9 months and up to nineteen years after operation, 22, or 52 per cent, had gastrojejunal ulcers. Lahey (1940),[285] who made a thorough study of this field, felt that the average incidence of gastrojejunal ulcer after gastroenterostomy is about 15 per cent. It should be said that in nearly all of these series, other cases were recorded as unimproved. Church and Hinton (1940)[89] felt that only 24.5 per cent of their gastric and duodenal ulcers subjected to gastroenterostomy could be considered as cured. Experimentally, Watts (1903)[515] has observed the spontaneous occurrence of jejunal ulcer in the dog after gastroenterostomy, and Dott and Lim (1923)[115] have recorded a high incidence of such ulcers after gastroenterostomy combined with pyloric occlusion.

A gastroenterostomy which is properly placed near the pylorus is commonly thought of as emptying by gravity drainage, yet the experimental work of Cannon and Blake (1905)[84] many years ago showed that the intra-abdominal pressure relationships made this impossible. If the pylorus remained patent, food went through the duodenum rather than the stoma, and Cannon and Blake observed that if the stomach was stretched by ingested material, obstruction might occur in the efferent loop by its compression against the gastric wall, thus resulting in the "vicious circle" which used to be seen so often clinically. Case (1925)[86] studied fluoroscopically patients who had had gastroenterostomies and found that in successful operations the emptying time was shortened to an average of three hours and forty minutes.

Burget and Steinberg (1922)[81] and Elman (1929)[135] observed that in dogs with posterior gastroenterostomies, duodenal regurgitation took place through the stoma, the stomach containing bile almost constantly, and acid test meals were rapidly neutralized (in sixty to ninety minutes). Herein was supposed to reside the beneficial effect of gastroenterostomy, and since high acidity seems to be the most important factor concerned in the development of jejunal ulcer, as will be developed later in this paper, the postoperative acidity should be of some importance. Holman and Sandusky (1938)[230] reviewed the literature on this subject, and found that a large number of writers claimed a reduction in acidity of 30 to 60 per cent, although some said there was no change; it was noted that most of these analyses had been done with various test meals and in a somewhat unstandardized manner. Holman and Sandusky, in their own series of seventy-four cases in which the gastric analyses were done by a standardized method using histamine, found that the reduction in gastric acidity fairly uniformly attained with gastric resection is not possible with gastroenterostomy.

Because of the high incidence of postoperative jejunal ulcers, gastro-enterostomy is very seldom employed by most surgeons in ulcer therapy today. It has not been abandoned, however, but is reserved chiefly for poor-risk cases, and especially those with obstructed atonic stomachs and low gastric acidity[286] since it is in this group that gastroenterostomy has given the best long-term results.

Gastric Resection.—

Gastroenterostomy versus gastric resection: While the evidence against gastroenterostomy delineated here was being accumulated, a long controversy raged in the surgical literature between the proponents of gastroenterostomy and those who favored gastric resection. European clinics, such as that of Haberer (1920),[200] and the University of Budapest (1926),[110, 111] on the basis of their own comparative studies found that the incidence of marginal ulcer after gastroenterostomy was excessively high and the results rather poor, and at a relatively early date they began to resect more stomach for ulcer. A. A. Berg (1928, 1930)[48, 49] was one of the early advocates of gastric resection in this country, and for many years was almost alone in this regard, the resistance to this radical approach to the ulcer problem being remarkably great throughout the country. Walters (1932),[495] as a result of comparisons he made between resected specimens seen in German clinics and similar specimens at the Mayo Clinic, felt that there was a geomedical difference between the ulcers seen in Europe, which were associated with a marked gastritis, and those in America, which were not. He thought gastric resection justifiable in Europe but not in this country. Jejunal ulcers after gastroenterostomy were explained as the results of a conservative procedure in patients in whom there was an associated gastritis. If this were true, the incidence of gastritis in America must be high indeed if Newburger's figures[383] are correct.

However, as the years passed by, more evidence accumulated that gastroenterostomy was a partial failure as a curative procedure for ulcer, and more surgeons were converted to the use of gastric resection. At present, the great majority of surgeons,[1, 104, 234, 290, 341, 508, 536] though perhaps differing as to the extent of resection, advocate gastric resection as the procedure of choice in most cases. A surprising exception is found in Heuer (1944)[217] and his associates. These writers, although admitting that probably only one-third as many jejunal ulcers occur after gastric resection as after gastroenterostomy, nevertheless felt this advantage of gastric resection was offset by the higher mortality of this operation in average hands, which they expressed as varying in the literature between 2 and 22 per cent, with a probable average of 7 per cent. However, Lewisohn (1945)[301] pointed out that in most experienced hands the mortality for gastric resection is only about 2 per cent. Indeed, on perusing the recent literature, some even lower mortality figures may be found, perhaps the result of the increasing number of valuable adjuvants to gastric surgery. For example, a mortality of 1.1 per cent is reported in 368 partial gastrectomies at the Mayo Clinic (1944);[98] Bartels and Dulin (1947)[38] reported 1.6 per cent mortality in 121 successive partial gastrectomies, and King (1946)[273] reported no deaths in a series of 75 subtotal gastrectomies. Zollinger[541] in 1940 made an extensive review of the literature in an effort to compare the results of gastroenterostomy and gastric resection, and recorded that the reported incidence of jejunal ulcer after gastroenterostomy varied between 2 and 24 per cent, while that after gastric resection varied between 0.4 and 10 per cent, which is rather convincing evidence that gastroenterostomy is not necessarily the more desirable procedure.

Altered physiology after gastric resection:

(1) Acidity. The beneficial effect of gastric resection for ulcer may be said to reside in (1) a diminution of the gastric acidity, (2) a removal of part or all of the "ulcer-bearing" portion of the stomach and duodenum, and (3) a decrease in the emptying time of the remaining stomach. Winkelstein and Berg (1938)[533] listed five factors which unite to determine the postoperative acidity after gastric resection. These factors were (1) removal of the antrum, abolishing the chemical phase (if Edkin's hypothesis is correct); (2) the extent of resection determining the amount of fundic secretory tissue removed; (3) the amount of regurgitation of duodenal fluids which occurred through the stoma; (4) the degree of vagus nerve irritability; and (5) the amount of gastritis present. These writers found that it was possible to produce achlorhydria by extensive resection in only 50 per cent of patients with duodenal ulcer with a high preoperative acidity, but stated that in twenty-six such patients in whom extensive resection was combined with unilateral vagotomy, achlorhydria was consistently produced.

What can be expected of gastric resection as concerns a reduction in acidity? Lewisohn and Ginzburg (1927)[302] reported that in a series of 85 subtotal gastrectomies, 64 patients had postoperative achlorhydria. Klein (1927)[274] reported that "partial" gastrectomy produced immediate hypoacidity or anacidity in 78 per cent of patients with gastric ulcer, but in only 18 per cent of patients with duodenal ulcer; however, after six months, these percentages rose to 100 and 66 per cent, respectively. Klein was unable to explain these later changes, but thought they might be due to a lowered vagus tone, or to a diminished irritability of the remaining parietal cells. Lake (1928)[293] found that achlorhydria was produced in 50 of 51 of his cases as a result of partial (half) gastrectomy; 97.5 per cent of these cases were classified as excellent results, and he stated that no jejunal ulcers developed in this series. All the patients studied by Shay and Gershon-Cohen (1936)[452] had achlorhydria after partial gastrectomy. The importance of the regurgitation of the intestinal contents at the stoma was emphasized by St. John's group (1939),[430] who found that in 26 resections, bile was present in the stomach in all except 2, that the peptic activity of the gastric contents was markedly reduced in all, and that free hydrochloric acid was absent in 22 cases, diminished in 3, and normal in 1. Lahey and Marshall (1937)[289] recorded that 64 per cent of their gastrectomized patients had postoperative achlorhydria or a free acid of less than 10 per cent.

It should be emphasized that most of these earlier studies were done using various test meals which are incapable of eliciting the maximum acid secretory response possible with histamine. Using histamine, Milanes (1936)[361] noted that 55 to 60 per cent of ulcer patients with subtotal gastrectomy developed achlorhydria. In 31 gastrectomized patients, Strauss and his colleagues (1937)[473] found achlorhydria to histamine in only 18 patients, but a marked reduction in acidity in 25; these workers felt that the clinical results were not correlated with the postoperative acidity, but it is noteworthy that the only patient with gastrojejunal ulcer in their series had a high postoperative acidity. Tomoda

and Aramaki (1938)[480] reported that after Billroth II resections the acidity was "in most cases" reduced or absent. The histamine analyses reported by Heuer and Holman (1943)[216] indicated that in 63 resections for duodenal ulcer, 17 patients were achlorhydric, 15 had a low acidity, and 31 had a high postoperative acidity, while in 25 resections for gastric ulcer, 18 had postoperative achlorhydria, 5 had a low postoperative acidity, and in 2 there was no change in the acidity. There was a considerable variation in the extent of these resections, explaining the marked differences in postoperative secretion. Heuer and Holman were unable to find any correlation between these acid values and the clinical results, and, since 3 of 11 patients with two-thirds or more of the stomach resected showed an acid response to histamine, but had good results, they felt that the chances of ensuring achlorhydria or better results by increasing the size of the resection beyond a moderate one were rather small. Lewisohn (1945)[301] recently stated that with a three-fourths to four-fifths resection of the stomach, anacidity was observed in 60 per cent of the patients after operation.

Patients who had had a variety of operative procedures for ulcer were studied by Wangensteen and Lannin (1942),[510] eliciting the maximum secretory response with three successive doses of 0.5 mg. of histamine. After only two procedures, namely, a three-fourths gastric resection with a Hofmeister retrocolic anastomosis, and a Finsterer three-fourths "resection for exclusion" with removal of the antral mucosa, was any significant percentage of achlorhydria found. With the first operation 52 of 82 patients showed achlorhydria, and 7 of 11 patients who had the second type of procedure showed it, both figuring out to be approximately 63 per cent. It is again noteworthy that in neither of these two groups of patients did any jejunal ulcers occur.

On the experimental side, the importance of the factor of neutralization was emphasized by the work of Portis and Portis (1926).[404] After subtotal gastrectomy in dogs, they found no free acid in the remnant of the main stomach, but a small Pavlov pouch continued to secrete free acid. Steinberg, Brougher, and Vidgoff (1927)[466] emphasized the same factor; by resecting the antrum, with gastrojejunostomy in dogs, they found the free acid was reduced or absent, but when the duodenal contents were then deviated to the terminal ileum, the acidity in the fundus promptly rose to high levels. If results in dogs are applicable to man, the work of Fauley, Strauss, and Ivy (1932)[150] and Shapiro and Berg (1934)[449] should temper enthusiasm for subtotal gastrectomy. Both of these groups emphasized that the gastric acidity returned to normal levels several months after a subtotal gastrectomy. Shapiro and Berg thought the size of the stoma was especially important as an influence on the amount of regurgitation (and thus dilution and neutralization) that occurred.

(2) Emptying Time. The x-ray findings of Case (1925)[86] indicated that the emptying time is markedly decreased after gastric resection; he noted an average emptying time of fifteen minutes to one hour after a Billroth I resection, but an emptying time of four and one-half hours after a Polya modification of the Billroth II procedure. Both experimental and clinical observations made by Mecray, Barden, and Ravdin (1937)[348] indicated that if hypopro-

teinemia is present, it may result in nutritional edema at the stoma, and a marked prolongation of the emptying time after resection. While fairly rapid emptying is desirable, and a relatively large stoma important in relation to the neutralization of acid by regurgitation of intestinal contents through the stoma, and also important in preventing a "jet effect" producing trauma to the intestine, it has been pointed out by Custer, Butt, and Waugh (1946)[103] that if the stoma is too large the so-called "dumping syndrome" may ensue. This syndrome, the result of excessively rapid emptying, and perhaps in part a manifestation of resultant hyperinsulinism, is characterized clinically by nausea, weakness, warmth, sweating, and palpitation, which occur after meals, and are relieved by lying down. In a series of 500 gastric resections, these authors found 28 such cases, an incidence of 5.6 per cent, and on the basis of this information advocated the Hofmeister type of anastomosis in preference to the larger stoma of the Polya anastomosis.

There is some evidence that the gastrojejunostomy stoma after resection of the stomach develops some degree of sphincter-like activity. Vitkin (1940),[493] studying resected patients fluoroscopically and resected dogs by means of balloons placed at the anastomosis through a gastric fistula, noted that there was a rhythmic evacuation of the gastric remnant occasioned by a periodic opening and closing of the anastomosis, due to peristaltic contraction of the efferent loop. Schindler and Dailey (1941)[442] have observed such sphincter-like contractions of the stoma through the gastroscope. Kennedy, Reynolds, and Cantor (1947)[267, 268] speak of the "true stoma" as being "not the circumference of the residual stomach, but only that narrowed jejunal diameter into which the stomach empties, found at the lower end of the anastomosis." They have demonstrated both by x-ray view and at operation (for incisional hernia four years after resection), contraction of the circular fibers of jejunal musculature in this area in a sphincter-like manner, with some out-pouching of the proximal "jejunal wall of the stomach." They arrived at the conclusion that the size of the true stoma remains the same (that is, the caliber of the jejunum) regardless of the type of anastomosis.

(3) Extent of Resection. With certain exceptions, the opinion that gastric resection is the elective procedure of choice in most cases of gastric and duodenal ulcer is fairly uniform, but there is less unanimity of opinion with regard to the extent of the resection necessary to prevent recurrence of the disease. Graham (1938)[179] advocated a resection of three-fourths of the stomach, noting that of the four jejunal ulcers which occurred in his series of gastric resections, three were in patients who had limited resections. The Lahey Clinic group (1937)[331] likewise believed a resection of three-fourths to four-fifths of the stomach is necessary, and Marshall (1945)[330] quoted illustrative cases of gastrojejunal ulcer after lesser resections. Hunt (1941),[234] however, believed that such a radical resection interferes too much with the function of the stomach as a reservoir, and felt that in the ordinary case, hemigastrectomy will provide reasonable assurance that jejunal ulcer will not occur, but in cases with excessively high gastric acid he believed in a more radical procedure. Likewise, Sanders (1945)[436] resected only about one-half of the stomach for ulcer, but

admitted an incidence of 8 per cent jejunal ulcers after operations for duodenal ulcer.

A detailed analysis of eighty-eight resections for gastric and duodenal ulcer by Holman and McSwain (1943)[229] indicated that all but one of their eleven patients with two-thirds of the stomach resected had achlorhydria or low acidity, and only 25 per cent of those with antral resection had lowered acid. Since they indicated that jejunal ulcers occurred only in those with a free HCl over 60 per cent after resection, their conclusion that the clinical results show no relation to the postoperative acidity is rather surprising. Even more surprising is their conclusion that the clinical results were not related to the extent of resection, although they indicate that there were no unsatisfactory results in the group with two-thirds or more of the stomach resected. It was stated by Bartels and Dulin (1947)[38] that in their experience more patients had achlorhydria after resection of less than two-thirds of the stomach than in the group with a more radical resection. This is quite surprising, in view of what is known concerning the physiology of the stomach. However, they admitted that recurrent ulcers are more frequent after conservative than after the more radical resections.

Rienhoff (1945)[416] prefered a rather conservative resection, going no higher than the incisura angularis on the lesser curvature. With this procedure 40 per cent of his patients were achlorhydric after operation, and most of them symptom-free, and he thus concluded that the success of gastric resection for ulcer depends chiefly on the permanent reduction in gastric acidity. An incidence of 9 per cent jejunal ulcers is claimed by Rienhoff, but Wangensteen (1945),[508] analyzing Rienhoff's own figures, noted that if the patients with episodes of gastrointestinal bleeding after operation were added to the number of proved marginal ulcers, this figure would reach approximately 21 per cent, and, in addition, another 16 per cent had sufficient pain to be classified as poor results.

In this connection, some experimental work done at the University of Minnesota is of interest. Baronofsky and his colleagues (1945)[35] performed resections of the Billroth I type of varying extent in dogs; 75 per cent of the dogs with either one-fourth or one-half of the stomach resected developed ulcers when injected repeatedly with histamine-in-beeswax, but a three-fourths resection protected all of the dogs from histamine-induced ulcer. Likewise, Lannin (1945)[295] in similar experiments showed that a three-fourths resection of the Billroth II variety would protect dogs against histamine-induced jejunal ulcers, while resection of one-half or less of the stomach would not. This experimental evidence has been repeatedly emphasized by Wangensteen (1941-1945),[503, 507, 510] who observed on the basis of his clinical experience that only after a resection of three-fourths or more of the stomach can one achieve as high an incidence of achlorhydria as 63 per cent. Moreover, he claimed that in his experience jejunal ulcers almost never occur after such an extensive procedure.

Most surgeons realize quite well the difficulty encountered in estimating the percentage of the stomach removed at the operating table. No absolutely

accurate method has been devised for doing this, but Wangensteen's group (1940)[512] believed that they can make a fairly close estimate by dividing the stomach into a series of rectangles and triangles and measuring these. In addition, they attached considerable importance to the weight and area of the tissue removed, believing that, unless the stomach is tremendously enlarged, the removal of 200 sq. cm. (measured on the serosal surface) is adequate, as is the removal of 180 to 220 Gm. of gastric tissue.

(4) Varieties of Gastric Resection. The original Billroth I operation, consisting of the removal of a portion of the stomach and the pylorus, and performing a gastroduodenostomy or one of its modifications, would appear to preserve the normal physiologic relationship better than other methods, providing relatively normal stimulation of pancreatic and biliary secretory activity.[408] However, Walters (1937)[497] has shown that a greater reduction in acidity is obtained with some modification of the Billroth II procedure than can be obtained with the Billroth I procedure. Since the experimental work of Lannin (1945)[295] and Baronofsky's group (1945)[35] has confirmed the clinical impression that an extensive resection is necessary to prevent ulcer recurrence, most surgeons, like Lahey (1939),[290] feel that the Billroth I operation might be unsafe, especially in cases of duodenal ulcer with edema and induration of the duodenum, since the anastomosis might be made under tension, or the operator might reduce the extent of the resection in order to insure an anastomosis without tension. Consequently, most surgeons[6, 179, 287, 508] prefer some modification of the Billroth II technique in which the duodenal stump is closed and the jejunum anastomosed to the stomach remnant. The modifications most frequently used are the Polya operation, with an end-to-side anastomosis, the stoma being the entire width of the lumen of the stomach remnant, or the Hofmeister modification of the Polya operation in which a portion of the gastric remnant is closed and the anastomosis made with the remainder. Evidence that one of the variants of the Billroth II type of anastomosis should be preferable to the Billroth I variety was contributed by Steinberg and Proffitt (1932),[467] who found that they could prevent ulcer formation in dogs which had the Exalto short-circuiting procedure (vide supra) by performing a subtotal gastrectomy with a Polya or Hofmeister anastomosis, while a Billroth I anastomosis resulted in ulcer development despite the extensive resection. This result was attributed to the mechanical "jet effect" due to the relatively small stoma of the Billroth I anastomosis. It appears[290] to make little difference whether the afferent loop is placed on the lesser curvature or greater curvature sides, but great importance has been attached to the length of the afferent loop; this will be discussed in a later section.

In certain cases of duodenal ulcer, particularly those involving the common duct in the inflammatory process, or surrounded by a diffuse inflammatory reaction, removal of the pylorus and of the ulcer is difficult or impossible without damaging vital structures. In this type of case, Finsterer (1931)[155] advocated "resection for exclusion," performing a variation of the Polya anastomosis but not removing the pylorus and pyloric antrum. Although he felt

that he obtained 90 per cent good results with this procedure, various surgeons[5, 287, 465] have noted a high incidence of jejunal ulcer after this procedure, one of the highest figures being 41 per cent quoted by Ogilvie (1938).[385] Allen and Welch (1946),[6] Wangensteen (1942),[504] and others practice such a procedure in difficult cases, but stress the importance of removing the antral mucosa in order to prevent jejunal ulcer. Moore (1947)[367] described a patient who had evidence of marginal ulcer despite repeated "resections for exclusion," but when the antral mucosa was removed, he recovered. Wangensteen and Lannin (1942)[510] called attention to the unsatisfactory clinical results after resection for exclusion if the antral mucosa is not removed. It is interesting that in Lannin's (1945)[295] series of experiments, dogs with a Finsterer "resection for exclusion," in which three-fourths of the stomach was removed, failed to develop ulcers after injections with histamine-in-beeswax, whether or not the antral mucosa was removed. However, in the hands of Pearse and Schilling (1947),[398] 90 per cent of their dogs which had a two-thirds gastric resection with the pyloric antrum left intact developed jejunal ulcer after histamine injections, but only 25 per cent of dogs with the same resection with removal of the pylorus developed histamine-induced ulcers.

Removal of a triangular portion of the stomach from the greater curvature side, or fundusectomy, was proposed by Connell (1929-1932),[94-97] because he felt that such a procedure carried an insignificant risk and still removed a considerable amount of acid-producing tissue. However, his quoted mortality rate was 14.3 per cent and one recurrence occurred in fourteen cases. His experimental work on dogs indicated that, while the gastric acidity was considerably reduced soon after the operation, it later returned to normal values. Watson (1935),[514] as well as Seely and Zollinger (1935),[447] also noted that after such procedures in dogs, the reduction in acidity was only temporary. Strangely enough, Fauley and Ivy (1936)[148] found that such a procedure prevented ulcer formation in a considerable number of their Mann-Williamson dogs and Lannin (1945)[295] observed that, although fundusectomy alone failed to prevent histamine-induced ulcers, fundusectomy combined with gastrojejunostomy appeared to furnish protection against the histamine-induced ulcer. This combination of fundusectomy and gastrojejunostomy has been performed in eight patients in Wangensteen's clinic.[297] Although achlorhydria was achieved in only two of these patients, no postoperative jejunal ulcers were reported in the follow-up study.

Believing that neutralization of acid by regurgitation of intestinal juices was the chief factor of success in any operation designed to ablate the ulcer diathesis by lowering the gastric acidity, Devine (1925)[113] recommended a pyloric exclusion with gastroenterostomy, without removal of any portion of the stomach. Such a procedure was modified by Bancroft (1932)[32] to include removal of the antral mucosa. However, all the experimental evidence indicates that this procedure is of little value. Grindlay (1941)[194] noted an increase in the gastric acidity in dogs after such a procedure. In attempting to devise a method of cholecystogastrostomy which would prevent cholangitis, Sandblom and his colleagues (1936)[435] and Gentile (1935)[174] performed such a procedure in conjunction with anastomosis of the gall bladder to the excluded antrum, and

observed an incidence of jejunal ulcer in their dogs of 35 and 24 per cent, respectively. Lannin's work (1945)[295] indicated that this pyloric exclusion operation failed to prevent histamine-induced jejunal ulcers. Graham (1938)[178] observed jejunal ulcers in three of four patients with such procedures.

Many years ago, an enteroenterostomy between the afferent and efferent jejunal loops was recommended by Braun (1892)[78] as an adjunct to gastroenterostomy to avoid stagnation in the proximal loop. This has since been utilized in conjunction with gastric resection,[465] but it has been recorded by Walters (1936)[496] that there is less reduction of acidity when such an enteroanastomosis is added to gastric resection than with an ordinary resection alone, and clinically such a procedure predisposes to the development of jejunal ulcer.[8, 285] As Lahey (1940)[285] has so wisely observed, "Any operation by which the alkaline jejunal contents are prevented from going back into the stomach to lower acidity predisposes to the occurrence of gastro-jejunal ulcer." Such an observation is strengthened by the evidence[8, 28, 47, 199, 288] that the Roux en-Y anastomosis in conjunction with gastroenterostomy or gastric resection predisposes to jejunal ulcer. The disappointing results of the Schmilinsky procedure (total intragastric regurgitation of duodenal contents), apparently due to a prolongation of the gastric phase of acid secretion, have already been noted.

JEJUNAL ULCER

General Observations

Throughout the literature the terms "marginal ulcer," "stomal ulcer," "gastrojejunal ulcer," and "jejunal ulcer" are used more or less synonymously. Hutchison (1919)[237] believed that the ulcers indicated by these terms included two varieties, the true jejunal ulcer, which he thought due to hyperacidity, and the anastomotic ulcer, which he thought due to nonabsorbable suture material. Walton (1925)[500] felt that all of these ulcers started from the anastomosis, even though this might not be evident in the resected specimen. Graham and Lewis (1935)[180] recorded that only one in their series of forty-three "marginal" ulcers was at the stomal suture line; all the others involved the jejunum only. The work of Ginzburg and Mage (1938)[176] indicated that at least 50 per cent of these postoperative ulcers involved the jejunum only, and most of these occurred in the efferent loop. When one considers the fact that by far the greater majority of experimentally produced postoperative ulcers are in the jejunum presenting an intervening area of relatively normal jejunal mucosa (vide supra), it seems rational to refer to these ulcers by the more accurate term of "jejunal ulcer."

Primary benign jejunal ulcer is exceedingly rare,[144] and jejunal ulcer seems to occur usually when unprotected jejunal mucosa is bathed by acid gastric juice as a result of some operative procedure such as gastroenterostomy or a variant of the Billroth II type of gastric resection. These ulcers are usually single, usually smaller than the ordinary peptic ulcer, and usually situated on the anterior surface of the jejunum close to the anastomosis.[288] Like the ulcers found in Mann-Williamson dogs, they are more frequent in the efferent loop

or opposite the stoma. They most frequently occur in patients who show evidence of high gastric acidity[180, 236, 331] and are quite rare in patients with achlorhydria, although such cases have been reported.[143, 518] Graham and Lewis (1935)[180] felt that the gastric analyses in such reported cases might be open to criticism, perhaps on the grounds that the position of the tube was not ascertained radiographically. Likewise, jejunal ulcers are extremely rare after resection for gastric ulcer,[178, 271] although Ransom (1947)[413] reports an incidence of 3 per cent after such operations. This fact must be taken into consideration in evaluating reports of the incidence of jejunal ulcer in mixed series of operations for gastric and duodenal ulcer. Jejunal ulcer almost never occurs after resection for gastric carcinoma,[178, 271] although Judd[257] and St. John's group[431] each reported such a case. Ninety per cent of postoperative jejunal ulcers occur in men, and they most frequently occur in the third or fourth decade.[292]

The Cause of Jejunal Ulcer

In a discussion of the etiology of postoperative jejunal ulcer, all of the factors concerned in the ulcer diathesis, as outlined in the section on etiology of peptic ulcer, must be given consideration, and all of these factors have had their champions. Mayo (1910),[336] Poole (1917),[401] Bastedo (1920),[39] Benedict (1933),[47] and many others attributed the development of jejunal ulcers after gastroenterostomy to the use of nonabsorbable sutures, since such sutures are sometimes noted in the base of these ulcers, or to the traumatic effect of clamps applied to the gut during the operative procedure. However, Judd and Hoerner (1935)[260] and Lewisohn (1925)[300] found that there was no change in the incidence of jejunal ulcer after gastroenterostomy when catgut was used exclusively. Montgomery (1923)[365] observed that the jejunal ulcers which occurred after gastroenterostomy in his dogs had no relation to the use of nonabsorbable sutures, and that the ulcers did not occur at the site of the clamps used during the operative procedure. Likewise, Scott (1929)[445] found that the ulcers in his Mann-Williamson dogs, in which the anastomoses were made with silk, did not occur at the anastomosis or in relationship to the silk sutures. Gallagher (1927, 1928)[168, 169] noted in dogs that acute lesions made by clamps in the mucosa of the jejunum, either in situ or transplanted into the stomach, healed quite rapidly, even when hydrochloric acid was injected into the stomachs of the animals.

Jejunal ulcer after gastric resection was ascribed by Birgfeld (1925)[63] to a triad of spasm, stasis, and hyperacidity. Steinberg and Starr (1934)[468] recorded that, when they did an Exalto short-circuiting procedure (deviating the duodenal contents to the ileum) in dogs, and, in addition, stripped the circular and longitudinal muscle fibers from the jejunum, except at the mesenteric border, no ulcers occurred, in the regions from which the muscle had been stripped. Moreover, they repeated the experiments of Matthews and Dragstedt (1932),[334] anastomosing the ileum to a Pavlov pouch, but stripping off the ileal musculature as before, and found that no ulcers developed in six dogs prepared in this fashion. They theorized that when acid entering the intestinal segment was too highly concentrated, the intestinal muscles contracted to hold it back, this spasm

resulting in local trauma and ulcer development. However, Fauley and Ivy (1937)[149] did similar experiments in conjunction with a modified Mann-Williamson procedure, and noted that the incidence of jejunal ulcer in these dogs was not influenced by stripping the jejunal musculature, and thus felt that the factor of spasm was unimportant. Some degree of importance in jejunal ulcer development has been ascribed to foci of infection by Grossman (1938)[196] and Wilkie (1934).[530] The mechanical or "jet effect" of a small stoma has received emphasis from Mann (1926, 1929),[322, 323] Morton (1927),[372] Fauley and Ivy (1931)[248] and Steinberg and Proffitt (1932).[467] However, the production of jejunal ulcers experimentally by numerous methods tending to prevent the neutralization of gastric acid, as detailed previously, emphasizes the tremendous importance of the factor of acid-peptic digestion. The importance of this factor is emphasized even more by the clinical evidence, indicating that jejunal ulcers are extremely rare after resections for conditions frequently associated with low acidity (gastric ulcer or carcinoma), or in achlorhydric patients. Nearly all modern clinicians[6, 291, 301, 385, 410, 507] accept the idea that the most important factor in the occurrence of jejunal ulcer after gastric resection is the impingement of acid gastric juice on a relatively unprotected jejunal mucosa. The degree of protection of this mucosa has been the concern of Wangensteen (1942-1945)[505, 506, 507] in his advocacy of the use of the short afferent loop in conjunction with gastric resection.

The Incidence of Jejunal Ulcer After Gastric Resection

The clinical literature dealing with gastric resection records an experience similar to that previously encountered with gastroenterostomy. Although Birgfeld[63] in 1925 was able to collect from the literature only fifty-one cases of jejunal ulcer after gastric resection, as the years passed by more and more cases were reported although the incidence has never reached the levels noted after gastroenterostomy. As Graham and Lewis (1935)[180] have observed, jejunal ulcers may occur shortly after the resection, or may manifest themselves for the first time many years later. Thus, reports giving a low incidence of jejunal ulcer after resection, based on short follow-up periods, or failing to indicate the length of the follow-up period, are of questionable value.

Lake,[293] in 1928, reported that no jejunal ulcers had occurred in a series of fifty-one of his cases with a hemigastrectomy; he felt that he could insure achlorhydria in most of his cases with this conservative procedure. In the same year, Strauss, Bloch, and Friedman (1928)[472] reported an incidence of less than 1 per cent jejunal ulcer after a high resection with Polya anastomosis. Starlinger (1930)[462] summarized 13,000 resections of the stomach for ulcer from various European clinics in 1930, and found an incidence of only 0.9 per cent recurrent ulceration after Billroth I procedures, and of only 0.6 per cent after Billroth II procedures. The collective inquiry by the Fellows of the British Association of Surgeons reported by Wright (1935)[537] elicited an incidence of only 1.9 per cent proved and suspected jejunal ulcers in 981 cases of partial gastrectomy. Gatewood (1930),[172] in a small series of thirty resections, reported three jejunal ulcers, or 10 per cent. As late as 1938, Ogilvie[385] reported that

he had had no recurrences in 100 cases of resection, and Miller (1942)[362] found no recurrences in a series of 230 subtotal gastric resections, although he did not state what type of procedure he used.

The experience of A.A. Berg's clinic is extremely interesting. Berg began performing subtotal gastric resection for ulcer in 1920, doing a radical three-fourths to four-fifths resection, with a short afferent loop (postcolic) anastomosis. In 1927, Lewisohn and Ginzburg[302] reported from Berg's clinic that no gastrojejunal ulcers had occurred in a series of 85 of these operations. In 1930, Berg[49] reported that in a series of 516 subtotal gastrectomies for gastric, duodenal, and jejunal ulcer, only 6 cases of probable jejunal ulcer had occurred, an incidence of 1.1 per cent. However, Mage (1942),[317] collecting the experience of the same clinic for the years 1923 through 1940, reported that in 502 resections for duodenal ulcer, there had been 33 instances of jejunal ulcer proved by operation, x-ray, or gastroscopic examination, and 7 other cases in which jejunal ulcer was strongly suspected because of massive painless gastrointestinal bleeding, thus giving an incidence of 7.9 per cent jejunal ulcer in the series of 502 cases.

The Relation of the Length of the Afferent Jejunal Loop to the Incidence of Jejunal Ulcer

On the basis of theoretical considerations and experimental work which will be outlined in the subsequent section, Wangensteen (1942-1947)[505, 506, 507, 509, 510] has repeatedly emphasized the importance of a short afferent jejunal loop in the prevention of jejunal ulcer after gastric resection. In a series of 300 patients with resections of three-fourths of the stomach, some of the Finsterer type (exclusion with removal of the antral mucosa), who had postcolic short afferent loop Hofmeister type anastomoses, he reported[505, 506, 510] that not a single recurrent ulcer had developed up to 1944, but in 1945 reported [507] one jejunal ulcer in the series, and in 1947[509] two in the series, an incidence of less than 1 per cent. Gaviser (1947)[173a] indicated that about 74 per cent of these resections were done for duodenal ulcer and that the follow-up period of the patients in this series varied between two and seven years.

The importance of the short afferent loop has been accepted by other surgeons, like Prohaska (1944),[410] who stated, "Even though the experiences of others with the anterior anastomosis has been yielding good results, I hesitate placing the anastomosis more distally in the jejunum because of the belief that the further distally we proceed from the stomach, the less resistant the intestine mucosa becomes to the gastric juice." A comparative series of cases, some with a long loop anastomosis, and others with a short loop, cannot be found in the literature, and attempts to evaluate this procedure from the clinical side for the present must be based on a comparison of the results of those who use the short loop method with the results of those who use the long loop. McClure and Fallis (1940),[341] reporting a series of seventy-four partially gastrectomized patients who had a short loop postcolic Hofmeister anastomosis, stated that six jejunal ulcers had occurred in the series, but they called attention to the fact that these six patients had had a limited resection, while all the patients with duodenal ulcer who had a more radical resection had excellent results. An

incidence of 2.5 per cent jejunal ulcer was reported by Walters, Lewis, and Lemon (1940)[498] in a series of 197 adequately followed gastric resections for duodenal ulcer, with short afferent loop postcolic anastomoses. Allen and Welch (1942, 1946),[5, 6] who do a similar type of short loop procedure, in 1942 reported no jejunal ulcers in a series of 71 resections for duodenal ulcer, but in 1946, in a series of 129 resections for duodenal ulcer, they reported 3 jejunal ulcers, an incidence of 2.3 per cent; in addition, there were 3 patients who had severe gastrointestinal bleeding, and 3 others who had pain sufficiently severe so that they were classed as poor results. If these 6 patients were assigned a presumptive diagnosis of jejunal ulcer, the incidence in Allen and Welch's later series would then be 7 per cent. Baker (1946),[30] utilizing a posterior short loop anastomosis, reported that no jejunal ulcers had occurred in his series of 105 resections for ulcer. In an analysis of 3 patients with jejunal ulcer, who had had their primary operations elsewhere, he felt that the chief factor involved was an afferent loop that was too long, stating, "_____ the shorter the proximal loop that is anastomosed, the greater the concentration of alkaline bile and pancreatic juices to bathe and protect the anastomosis."

At the Lahey Clinic, an extensive (three-fourths to four-fifths) resection of the stomach for ulcer is practiced, combined with an antecolic long loop Hofmeister anastomosis,[331] with the stoma twelve to sixteen inches past the ligament of Treitz. Lahey,[291, 292] although admitting that the incidence of jejunal ulcer is probably lower after a short loop postcolic anastomosis, has consistently advocated the antecolic long loop anastomosis because of (1) the greater ease of the technical procedure, (2) the diminished likelihood of involvement of the blood supply of the transverse colon if a jejunal ulcer should develop, and the diminished likelihood of gastrojejunocolic fistula, and (3) the relative ease with which a jejunal ulcer can be handled surgically, if it should develop after an antecolic anastomosis, as compared with the technical difficulty and hazards involved in surgical interference with a jejunal ulcer developing after a postcolic anastomosis. Of course, if, as Wangensteen believes, the incidence of jejunal ulcer after the short loop anastomosis can be reduced to an almost negligible fraction of a per cent, this argument would no longer be tenable. Lahey (1945)[287] stated that the average incidence of jejunal ulcer after gastric resection is 2 to 3 per cent, but the figures recorded from his clinic are higher than this. In 1937, Marshall and Kiefer[331] reported 5 jejunal ulcers in a series of 74 resections with antecolic anastomoses, an incidence of 6.7 per cent. In 1940, Kiefer[271] reported that, while 49 patients with a similar type of procedure done for gastric ulcer did not develop jejunal ulcer, in 173 patients with the same procedure done for duodenal or jejunal ulcer, there were 6 (3.4 per cent) jejunal ulcers proved at a later operation, and 6 others with an x-ray diagnosis of jejunal ulcer, a total incidence of 6.8 per cent. However, as Wangensteen (1944)[506] pointed out, if another 8 patients, who had upper gastrointestinal hemorrhage after such a procedure, but failed to show evidence of jejunal ulcer on x-ray examination, could be presumed to have jejunal ulcers, the incidence for the series of 173 cases would then be 11.6 per cent, and the incidence in the mixed series of 222 cases would be 9.0 per cent.

Graham (1938)[179] performed an extensive resection with a postcolic Polya type of anastomosis, but used a long afferent loop in order to avoid postoperative mechanical obstructive difficulties. With such a long loop procedure, in a series of 140 resections for duodenal ulcer, he reported 4 jejunal ulcers, an incidence of 2.9 per cent, but called attention to the fact that 3 of the 4 developed after limited resections, only 1 occurring after a truly radical resection. Church and Hinton (1942)[90] followed a series of 104 patients who had gastric resections for ulcer, the length of follow-up time averaging 2.8 years. Eighty-five per cent of these patients were operated upon for duodenal ulcer, and some of them had had the operations in other clinics. These authors found that none of their own patients, who had a two-thirds resection and a long loop antecolic anastomosis, developed proved jejunal ulcer, although 4 had clinical symptoms arousing the suspicion of the presence of such an ulcer. However, 2 patients in this group who had had limited resections elsewhere developed jejunal ulcer.

Recently King (1946)[273] reported 75 consecutive resections of two-thirds of the stomach for ulcer, with an antecolic long loop Hofmeister anastomosis, with only one recurrence (1.3 per cent). He, too, failed to indicate the site of the ulcer for which operation was indicated, or the length of the follow-up period. Kennedy and Reynolds (1946)[266] took issue with the thesis that a short afferent loop is important, in reporting 90 subtotal resections, including 21 for gastric ulcer, 1 for jejunal ulcer, and 68 for duodenal ulcer, without a single recurrence, these operations having been accompanied by an antecolic anastomosis with the stoma located 30 to 40 cm. from the ligament of Treitz. While they indicated that some of these patients had been followed five years, the length of follow-up in the remainder was not stated. An incidence of 1.8 per cent jejunal ulcers after subtotal resection for ulcer, with a long loop antecolic anastomosis, has been recently reported by Bruusgaard (1948).[79] He noted, however, that the follow-up period ranged from one to four years and felt that the incidence might increase with time. He also thought that his results would perhaps be improved if he used a shorter afferent loop.

THE RATIONALE OF THE SHORT AFFERENT JEJUNAL LOOP

On the clinical side, it is apparent that the evidence is somewhat conflicting as to whether or not a short loop anastomosis is the most desirable in the prevention of jejunal ulcer after gastric resection. The experimental evidence is much more convincing. In 1945, the University of Minnesota group (1945)[354] reported some experiments with dogs which present indications that the length of the afferent loop is an important factor in the development of jejunal ulcer. Two series of dogs were prepared by performing a subtotal (three-fourths) gastric resection, making an end-to-side Hofmeister gastrojejunal anastomosis. In the first series of eleven dogs, this anastomosis was performed as close to the closed end of the duodenal stump as was feasible, the distance from stoma to stump varying from 12 to 15 cm. After a rest period of three months, these dogs were injected daily with the histamine-in-beeswax mixture, receiving 30 mg. of histamine base each day, and after forty to forty-five daily injections were sacrificed. Not a single jejunal ulcer was noted in this series of dogs, although

two of them had superficial gastric erosions and one had a few small submucosal hemorrhages. In the second series of seven dogs, the same operation was done, except that the anastomosis was made at a distance from the inverted duodenal end varying between 27 and 78 cm. After the three-month rest period, histamine-in-beeswax injections were given daily. Three of these dogs died, at three, twelve, and twenty-two days, respectively, after the start of the injections, of peritonitis secondary to perforated jejunal ulcers. Two of these three had the longest (78 cm.) afferent loops. The remaining four dogs were sacrificed after either forty-five or forty-eight days of histamine injections, and all showed large jejunal ulcers, usually opposite the stoma. A third series of dogs received no histamine injections. Two of these had a hemigastrectomy with a long (78 cm.) afferent duodenojejunal loop. One was sacrificed 210 days after the operative procedure and no ulcer found, but the second dog died 420 days after the procedure of peritonitis secondary to a perforated jejunal ulcer. A third dog with a 60 per cent resection and an unusually long (144 cm.) afferent loop died, 338 days after the procedure, of peritonitis secondary to a perforated jejunal ulcer. A fourth dog with a 75 per cent resection and an afferent loop 90 cm. in length had, at the time of publication, survived 761 days after the procedure with no clinical evidence of ulcer.

The importance of the results in the last group of dogs may be minimized, because the resections in three of them were small, and the afferent loops were so ridiculously long that no clinical comparison is evident. However, the importance of the results in the first two group of dogs, as well as the direct clinical application of these results, is immediately obvious. If a three-fourths gastric resection, with a short afferent loop, will protect dogs from histamine-induced ulcers, while a three-fourths resection with a long afferent loop will not, it would seem logical to assume that the former operation would be more satisfactory in ridding man of the ulcer diathesis.

The University of Minnesota group (1945)[357] has also demonstrated the importance of the short loop anastomosis by the use of the Schmilinsky procedure, which has been discussed previously. In one series of eleven dogs, they excised the pylorus, closing the duodenal stump, and then sectioned the bowel 8 to 15 cm. from the stump. The aboral end of the intestine was used to make an end-to-end gastroenterostomy, while the oral end was anastomosed to the stomach above, thus providing complete intragastric regurgitation of the duodenal contents. These dogs were sacrificed at intervals varying from 82 to 360 days after the procedure, and only one of them was found to have developed a gastrojejunal ulcer. In a second series of six dogs, the same operation was done except that the length of the duodenojejunal loop varied from 76 to 90 cm. These dogs became irritable and languid, and died at intervals varying from 50 to 145 days after the procedure. Four of the six had perforated jejunal ulcers just distal to the efferent stoma, while one other had a large gastric ulcer on the greater curvature of the fundus, and the remaining dog had a severe gastritis, with scattered pin-point erosions. Thus it was thought that the variable results obtained with the Schmilinsky procedure by previous investiga-

tions were due to their use of duodenojejunal loops which varied considerably in length; neutralization was thought to be more complete when a short loop was used.

In his advocacy of the short afferent jejunal loop, Wangensteen (1942-1947)[505, 506, 507, 509] maintained that with such a short loop, neutralization of the remaining gastric acidity is improved, as compared with that after a long loop procedure, because of three factors. These are (1) the secretin factor, (2) the spatial separation between the biliary and pancreatic ducts and the gastrojejunal stoma, and (3) the increasing sensitivity or susceptibility of lower segments of bowel to the digestive activity of gastric juice. Each of these factors will be discussed in detail. A fourth factor, enterogastrone, has been entertained by Kolouch (1946)[278] but dismissed because of the fact that enterogastrone has been located in all segments of the bowel, including the colon. In a series of extremely complicated experiments, using the Schmilinsky procedure, but varying it in a number of ways by employing various lengths of bowel, various types of anastomosis, and interposing various segments of gut, Wangensteen's group (1945)[280] has attempted to evaluate the relative importance of these three aforementioned factors. Their attempts to separate the three factors were not entirely successful, and their conclusions from these experiments were somewhat uncertain, although they felt that the "sensitivity" factor had less importance than the other two. The operations were so complicated, so many variables were introduced, and the series of dogs (two for each type of operation) were so small, that this work lacks definitive significance.

The Secretin Factor

The importance of the pancreatic juice as an agent capable of neutralizing, buffering, and diluting hydrochloric acid has already been emphasized. The vagus nerve is thought to be the secretory nerve of the pancreas.[41] However, bilateral transthoracic vagotomy in experimental animals does not have any marked influence on the volume of pancreatic juice obtained through a pancreatic fistula.[446] The hormonal mechanism of exocrine pancreatic secretion is more important. Dolinski,[116] in 1894, discovered that an ingested solution of hydrochloric acid was an exceedingly strong stimulus of pancreatic secretion. According to Pavlov (1910),[397] Popielski showed that hydrochloric acid activated pancreatic secretion only when it reached the duodenum, and Wertheimer and Lepage found that this activity could be obtained from the duodenum, jejunum, and ileum (except for the last two feet), and that the effect diminished in intensity with descent in a caudal direction; they also showed that intravenous injection of hydrochloric acid had no effect on pancreatic secretion.

The experiments of Wertheimer and Lepage were repeated by Bayliss and Starling (1902).[44] The pancreatic duct was cannulated and a loop of jejunum isolated, with section of all nerves to it, to exclude the possibility of a reflex phenomenon. When acid was introduced into such a loop, pancreatic secretion was stimulated. The jejunal mucosa was extracted, and this extract when injected intravenously elicited a copious flow of pancreatic juice. The "secretin theory" was thus elaborated by Bayliss and Starling; they thought that contact

of hydrochloric acid with the epithelial cells in the duodenum caused the production of a hormone "secretin," by a process of hydrolysis from a precursor, "prosecretin," present in the cells; this secretin is absorbed into the blood stream and carried to the pancreas, where it acts specifically on the pancreatic cells, resulting in the production of pancreatic juice proportional in amount to the quantity of secretin in the blood.

The experiments of Mellanby (1926)[351] indicated that the cholic acid present in bile would produce this secretin effect when introduced into the small intestine. Mellanby and Huggett (1926)[352] confirmed the work of Bayliss and Starling, except that they felt that it was proved, by extraction with various substances, that secretin existed in the intestinal mucosa in the preformed state, and not as the precursor, prosecretin. While pancreatic juice obtained by them by vagal stimulation was rich in enzymes, and with prolonged vagal stimulation the pancreatic cells showed marked signs of exhaustion, the juice secreted in response to secretin was poor in enzymes, but was secreted in copious quantities, and the pancreative cells showed no signs of exhaustion after prolonged stimulation with secretin. No secretin was found in the gastric mucosa by these workers, but a considerable amount was found in the upper small intestine and only a slight amount in the lower small intestine and colon. Secretin has actually been isolated in the form of a crystalline picrolonate by Greengard and Ivy (1938)[186] from the mucosa of the upper six feet of the dog's intestine, and a quantitative response to the intravenous administration of this substance to dogs with pancreatic fistulas was determined by the same group (1941).[187]

Abundant experimental evidence has been cited by Pavlov (1910)[397] indicating that acid extracts of the upper intestinal mucosa will excite the flow of bile. Puestow (1931)[411] showed that bile was discharged into the duodenum shortly after acid chyme entered the small intestine. Although Pavlov felt that this excitosecretory effect was due to secretin, as did Still, McBean, and Ries (1931),[471] in their work with dogs with biliary fistulas, Ivy (1929),[242] after demonstrating by cross-circulation experiments that when N/10 HCl, as well as various fats and oils, were injected into the duodenum, something got into the blood stream which caused the gall bladder to contract, felt that this was a different hormone, and called it "cholecystokinin." More recently, Agren (1939)[2] has shown that secretin and cholecystokinin are different, and has prepared each free from the other. The work of Delezenne and Frouin, as reported by Pavlov (1910),[397] indicated that weak solutions of hydrochloric acid injected into one isolated duodenal loop produced a marked flow of succus entericus from another loop, and Pavlov thought that the mucosa of the duodenum might contain a "hormone of hormones," which he called "enterokinase."

Thus, it is apparent that the excitosecretory mechanism for these neutralizing and diluting secretions is dependent on acid reaching the intestinal mucosa. The work of Wertheimer and Lepage, Mellanby and Huggett and others indicates that this "secretin effect" diminishes as one passes caudalward in the intestinal tract. Wangensteen,[505, 506, 507] therefore, reasoned that the use of a more aboral segment of jejunum for the gastrojejunal anastomosis in a Billroth II

type of procedure would result in a diminished secretion of these substances capable of neutralizing, buffering, and diluting the remaining gastric acid, and thus with a more aboral anastomosis the incidence of postoperative jejunal ulcer would be increased. An attempt to determine this point directly was made by Kolouch (1946, 1947).[278, 279] He provided dogs with pancreatic fistulas, and after determining the pancreatic secretory response of each dog to a variety of enteral and parenteral stimuli, subtotal (three-fourths) gastric resections were done. Two series of three dogs each were used; in one series, the afferent jejunal loop was short, while in the other, it was long. The comparisons of the pancreatic secretion before and after these resections indicated that resection of the stomach caused a reduction in volume of the pancreatic secretion, and that this reduction was greater when a long afferent loop was used. However, Kolouch admitted that these results must be taken with some reservation, because the secretory responses to various stimuli were rather inconstant both before and after gastric resection.

The Spatial Factor

It was felt by Wangensteen[505, 506, 507] that the power of the pancreatic and biliary secretions and succuss entericus to neutralize, dilute, and buffer gastric acid would be diminished as the distance from their source to the gastrojejunal stoma increased.

Various studies of the acidity of the contents of the small intestine shed very little light on the subject. Mann and Bollman (1930)[325] studied the secretions of the contents of various segments of the intestinal tract in dogs by the use of fistulas made from a loop of ileum anastomosed to the exterior and to the portion of bowel to be studied. They found that while the content of the duodenum might be acid when highly acid values were found in the stomach, the usual reaction of the small intestine contents was alkaline (pH 7.0 to 8.0), and after a meal was about pH 6.5 to 7.5. Robinson (1935)[419] found that the pH was about 6.5 in the duodenum in dogs, and increased gradually in the aboral direction to about 7.5 or 8.0 at the ileocecal valve. He perfused segments of bowel from various levels with a number of different solutions, and found that regardless of the pH of the solution used, the pH of the solution which returned was relatively constant. The progressive increase in pH throughout the jejunum was thought due to a combined increase in bicarbonate and decrease in CO_2 tension.[420] Miller and Karr (1936)[363] studied the reaction of the intestinal contents of man at various levels by intubation, and found that the reaction of the jejunal contents was usually neutral, but when a strong stimulus to gastric secretion of acid, such as histamine, was administered, a more acid intestinal reaction resulted. McGee and Hasting (1942),[343] in similar intubation studies, found that the reaction of the jejunal contents in man was slightly acid (pH 6.5) and when this value was changed by the introduction of acid or alkali, it returned to the normal level fairly promptly.

In dogs, Wu (1935)[538] studied the reaction of the jejunal contents 5 to 10 cm. below the ligament of Treitz by means of Mann fistulas, and found that in the fasting state the pH at this point usually varied from 7.6 to 8.1 (with

extremes of 6.9 to 8.3), and after a meal varied from 7.0 to 7.8 (with extremes of 5.2 to 8.2). He then performed the Mann-Williamson surgical duodenal drainage procedure in these dogs, sectioning the jejunum a short distance above the fistula he had already created, and after this procedure again made pH determinations. The acidity was found to be markedly increased, the pH in a fasting state varying between 5.5 and 7.9 (with extremes of 2.4 to 8.3), and, after feeding, varying from 5.2 to 6.9 (with extremes of 1.7 to 8.3). This work gave some quantitative indication of the neutralizing and buffering value of the duodenal juices at a point 5 to 10 cm. below the ligament of Treitz.

The loss in titratable alkalinity of a solution similar in composition and buffering value to the pancreatic juice of a dog when perfused through intestinal loops of various lengths was determined by Kolouch (1946)[278] in dogs. After excluding the duodenal juices by ligating the duodenum distal to the entrance of the pancreatic ducts, or by ligating the pancreatic and common bile ducts, loops of jejunum were isolated by ligating each end of the loop. One catheter was inserted in the proximal end of the loop, and another in the distal end; 50 c.c. of the prepared solution of known alkalinity was dripped through the proximal catheter in a period of two hours, and withdrawn from the distal catheter by gravity and suction. The volume of the solution withdrawn was measured, and again titrated with 0.1 N HCl. It was found that the alkaline solution lost volume and a large quantity of its buffering capacity in its passage through the loop of intestine; when the solution was passed through long (38 to 49.5 cm.) segments of gut, the reduction in volume and buffering capacity was much greater than when it was passed through a short (10 cm.) loop, thus supporting Wangensteen's thesis.

Weiss, Graves, and Gurriaran (1932)[520] varied the Schmilinsky procedure so that the duodenal contents were introduced into the stomach immediately adjacent to the efferent gastrojejunal stoma. Although McCann (1929)[339] obtained jejunal ulcers in 80 per cent of his dogs, when the duodenal loop was anastomosed to the fundus, Weiss and his associates found that with their procedure not a single ulcer occurred in fourteen dogs. The spatial factor in such procedures was emphasized by Maier and Grossman (1935),[318] who felt that, in the Schmilinsky procedure, when the duodenal loop was anastomosed to the fundus, a considerable portion of the alkalinity was lost for neutralization at the stoma. They felt that the acid values obtained in gastric analysis after gastric resection were overemphasized, since the pH of the efferent jejunal loop should be the important consideration in relation to the development of jejunal ulcer, and this pH is the result of the interaction of the gastric chyme and the alkaline contents of the afferent loop at the stoma. It should be recognized, however, that in experiments based on the Schmilinsky procedure, the same conditions do not obtain as are found in the afferent loop after gastric resection, because acid is constantly being secreted by the gastric mucosa, and whether or not jejunal ulcers develop is not necessarily a result of the spatial separation of duodenal secretions from the efferent stoma.

The site of duodenal drainage in Mann-Williamson dogs was varied from close to the gastrojejunostomy stoma to the distal ileum by Gallagher and

Palmer (1932).[171] They reported no relationship between the site of drainage and the incidence or rapidity of ulcer formation. Wilhelmj, O'Brien and McCarthy (1936)[529] repeated the Mann-Williamson procedure with the duodenum drained into the jejunum only a short distance below the gastrojejunal anastmosis. In four dogs, no ulcers occurred, and the regurgitation of the duodenal contents to the stoma was indicated by the presence of bile in the stomach. Thus, it would appear that the distance separating the source of the duodenal secretions from the gastrojejunostomy stoma may have some importance in jejunal ulcer prevention.

The Sensitivity Factor

There is a considerable amount of evidence available indicating that the lower segments of small bowel are more susceptible to the digestive activity of gastric juice. The frequency of ulcer formation in the mucosa of the ileum adjacent to a Meckel's diverticulum, when that diverticulum contains actively secreting gastric mucosa, has been pointed out by Aschner and Karelitz (1930),[19] and Lindau and Wulff (1931).[310] Kogut and Stein (1936)[276] collected from the literature a series of thirteen cases in which unintentional gastroileostomy had been done, and added three cases of their own, noting that in these sixteen cases, four patients developed gastroileac ulcers and another had a severe gastroileitis. De Takats and Mann (1927)[112] have noted in dogs that when an isolated segment of jejunum, with its blood supply intact, is opened up and transplanted into the gastric wall, a number of these animals will develop ulcer in the transplanted jejunum, especially if the transplantation is in the region of the lesser curvature.

Langeskiold (1914),[294] in acute experiments with dogs, perfused segments of duodenum and jejunum with various solutions, including natural gastric juice, and dilute hydrochloric acid, for various lengths of time, and concluded on the basis of his results that the upper part of the duodenum was probably more resistant to gastric juice than the lower portion of the duodenum and jejunum. The work of Langeskiold was recently repeated, with modifications, by Schiffrin and Warren (1942),[441] who concluded that, in the absence of the bile and pancreatic secretions, the duodenum was more susceptible to acid alone than either the jejunum or ileum, and that the susceptibility of the latter two was about equal. Matthews (1931)[333] found that in dogs he could consistently produce ulcers in the ileum by making an anastomosis between a Pavlov pouch and a loop of ileum. Fauley and Ivy (1929, 1931)[146, 248] varied the Mann-Williamson procedure by dividing the duodenum one inch distal to the pylorus; after sectioning the jejunum twelve inches below the ligament of Treitz, the aboral end of the jejunum was anastomosed to the proximal end of the duodenum (the distal end being closed), and the oral end of the jejunum anastomosed to the terminal ileum. All of their dogs developed ulcers, but in each case these ulcers were not in the one inch of duodenum adjacent to the pylorus, but in the first portion of the anastomosed jejunum. They felt that this indicated that the mucosa of the jejunum was more susceptible to digestion by gastric juice than that of the duodenum.

The work of McMaster (1934)[345] is of special interest in this connection. In dogs, he sectioned the stomach 1 cm. proximal to the pylorus, closing the distal end. The proximal end was used to make a gastroenterostomy, using various segments of bowel in various dogs. Of 4 dogs with gastroduodenostomy no ulcers developed; of 11 dogs with gastrojejunostomy, 5 (45.4 per cent) developed jejunal ulcers distal to the anastomosis; of 10 dogs with gastroileostomy 7 (70 per cent) developed ileal ulcers just distal to the anastomosis. This work seemed to indicate not only that there was an aboral gradient of increasing susceptibility of the intestinal mucosa to digestion by acid gastric juice, but it may have also suggested the importance of the spatial separation of the duodenal secretions from the anastomosis.

Fistulas of the Mann type to the stomachs of dogs, using loops of ileum, were made by Goldberg (1932),[177] and when the portions of stomachs containing the fistulas were later converted to pouches, each dog developed an ulcer in the ileal segment, and many of the ulcers perforated. Goldberg's work was continued by Harper (1932, 1935),[207, 208] using different segments of bowel to fashion the fistulas. He reported that when the duodenum was used for the fistula, ulcers formed but did not perforate; when the jejunum was used, the average life of the dogs before they died of perforated jejunal ulcer was 71 days, and when the ileum was used, the average life before perforation was 23 days. This seemed to indicate an increasing vulnerability of the lower segments of small bowel to gastric juice. Using the hog as an experimental animal, Florey's group (1939)[158] performed somewhat similar experiments and failed to obtain ulcers when the duodenum was used to fashion the fistula between the Pavlov pouch and body wall, but obtained ulcers in every animal in which the ileum was employed.

Driver, Chappell, and Carmichael (1945)[127] in acute experiments resembling those of Langeskiold, perfused loops of the dog's jejunum, at different levels with varying strengths of pepsin dissolved in N/10 HCl, varying the length of time of perfusion from four to thirty hours. They, too, found that the more distal loops of jejunum were more susceptible to the action of the acid-peptic mixture than the more proximal loops, and therefore felt that gastrojejunal anastomosis should be done as close to the ligament of Treitz as possible. However, results conflicting with these were obtained in the recent acute experiments of Kolouch (1946),[278] who exposed various pedicled exteriorized segments of bowel, from stomach to colon, to a drip of acid-pepsin mixtures, buffered to a pH equal to that of gastric juice, and found that while the gastric mucosa was quite resistant to the corrosive action of these mixtures, the susceptibility of the mucosa of the duodenum, jejunum, ileum, and colon to the acid peptic digestion was about equal.

In summary, then, while it is not entirely clear as to whether the secretin factor, the spatial factor, or the sensitivity factor is the most important, there is a large volume of experimental evidence indicating that the closer a gastrojejunal anastomosis is made to the duodenum, the less likelihood there is that the ulcer diathesis will persist.

SUMMARY

A review of recent literature dealing with certain important physiologic aspects of gastric surgery, as well as with theories of ulcer causation, has been presented, indicating the long-term results which may be expected from various operations, with particular regard to subtotal gastric resection, and the type of gastric resection which should be most preferable.

CONCLUSIONS

1. Physiologic and anatomic studies to date indicate that the pyloric antrum secretes little or no hydrochloric acid. The hormonal or "gastrin" theory of gastric secretion has been fairly well substantiated although there is some difference of opinion concerning this among physiologists; at any rate, better clinical results are obtained when the pyloric mucosa is removed than when it is left in place. The weight of evidence indicates that gastric juice is secreted at a constant degree of acidity (0.5 per cent or .16 N HCl), and that the gastric acidity is lowered by the normal progress of regurgitation of alkaline duodenal contents. An operation for ulcer which is physiologically justifiable should provide for such a process of neutralization.

2. From the available evidence, it would appear that subtotal gastric resection offers the best long-term results of any operation in use at present in the elective surgical treatment of benign gastric and duodenal ulcer. The procedure of choice appears to be a resection of three-fourths or more of the stomach, including the pyloric mucosa, with a Hofmeister type of gastrojejunal anastomosis made as close as is technically possible to the duodenum. The procedure of vagotomy appears to be promising in selected cases, but its permanent place in ulcer surgery remains to be evaluated.

REFERENCES

1. Abell, I.: The present status of gastrectomy, Am. J. Digest. Dis. **7**: 495-498, 1940.
2. Agren, G.: On the preparation of cholecystokinin, Skand. Arch. Physiol. **81**: 234, 1939.
3. Allen, A. W.: Surgical treatment of duodenal ulcer, Arch. Surg. **44**: 501-519, 1942.
4. Allen, A. W.: Gastric ulcer and cancer, Surgery **17**: 750-754, 1945.
5. Allen, A. W., and Welch, C. E.: Gastric resection for duodenal ulcer—Follow-up studies, Ann. Surg. **115** 530-543, 1942.
6. Allen, A. W., and Welch, C. E.: Subtotal gastrectomy for duodenal ulcer, Ann. Surg. **124**: 688-707, 1946.
7. Alley, A.: The inhibitory effect of histamine on gastric secretion, Am. J. Dig. Dis. and Nutr. **1**: 787-794, 1935.
8. Alvarez, W. C.: Light from the laboratory and the clinic on the causes of peptic ulcer, Am. J. Surg. **18**: 207-231, 1932.
9. Alvarez, W. C.: What value has gastric analysis? Gastro-enterology **1**: 534-536, 1943.
10. Alvarez, W. C., Hosoi, J., Overgard, A., and Ascanio, H.: The effects of degenerative section of the vagi and the splanchnics on the digestive tract, Am. J. Physiol. **90**: 631-655, 1929.
11. Anderson, A. C., Slutzky, B., and Moertz, R. W.: Effect on gastric secretion of pedicle jejunal grafts in the wall of the stomach, Gastroenterology **4**: 323-331, 1945.
12. Andresen, A. F. R.: Results of treatment of massive gastric hemorrhage, Am. J. Dig. Dis. **6**: 641-646, 1939.
13. Andrus, W. D., Lord, J. W., and Stefko, P.: Comparative effects of gastroenterostomy and pedicle jejunal graft on the pH of gastric mucosa, Proc. Soc. Exp. Biol. and Med. **52**: 99-100, 1943.
14. Andrus, W. D., Lord, J. W., and Stefko, P.: Effects of pedicle grafts of jejunum in the wall of the stomach on gastric secretion—Experimental and Clinical studies, Ann. Surg. **118**: 499-522, 1943.

15. Andrus, W. D., Lord, J. W., Stefko, P., and Dingwall, J. A.: The effect of saline washings of isolated jejunal loops on gastric secretion, Am. J. Physiol. **140**: 287-290, 1943.
16. Andrus, W. D., Lord, J. W., and Stefko, P.: A possible mode of action of pedicle jejunal grafts in gastric secretion, as indicated by changes in pH of surface of the mucosa of the stomach, Am. J. Physiol. **141**: 75-77, 1944.
17. Apperly, F. L.: Duodenal regurgitation and the control of the pylorus, British J. Exper. Path. **7**: 111-119, 1926.
18. Apperly, F. L., and Norris, J. H.: The automatic regulation of gastric acidity, J. Physiol. **70**: 158-168, 1930.
19. Aschner, P. W., and Karelitz, S.: Peptic ulcer of Meckel's diverticulum and ileum, Ann. Surg. **91**: 573-582, 1930.
20. Aschoff, L.: Lectures in pathology, pp. 279-312, Paul B. Hoeber, Inc., 1924.
21. Babkin, B. P.: The physiological factors determining the acidity of the gastric juice and of the gastric contents, Canad. M. A. J. **17**: 36-42, 1927.
22. Babkin, B. P.: The acidity of the gastric juice, Am. J. Surg. **7**: 498-504, 1929.
23. Babkin, B. P.: The chemical phase of gastric secretion and its regulation, Am. J. Dig. Dis. & Nutr. **1**: 715-721, 1934.
24. Babkin, B. P.: The abnormal functioning of the gastric secretory mechanism as a possible factor in the pathogenesis of peptic ulcer, Canad. M. A. J. **38**: 421-429, 1938.
25. Babkin, B. P.: The triple mechanism of the chemical phase of gastric secretion, Am. J. Dig. Dis. **5**: 467-471, 1938.
26. Babkin, B. P.: Secretory mechanism of the digestive glands, Paul B. Hoeber, Inc., 1944.
27. Bachrach, W. H., Schmidt, C. R., and Beazell, J. M.: The relation of bile and pancreatic juice to duodenal ulcer in dogs, Proc. Soc. Exper. Biol. & Med. **40**: 322-324, 1939.
28. Baggio, G.: L'influenza che sulla produzione dell'ulcera del digiuno viene esercitatu dalla deviazione del contenuto duodenale, Ann. Ital. Di Chir. **3**: 583, 1924.
29. Baggio, G.: Experimental gastric ulcer from obstruction to the emptying of the stomach, International Abstract of Surgery, **44**: 490, 1927.
30. Baker, J. W.: Gastro-jejunal ulcer following gastric resection, West. J. Surg. **54**: 341-345, 1946.
31. Balfour, D. C.: The occurrence and management of gastrojejunal ulcer, Ann. Surg. **84**: 271-280, 1926.
32. Bancroft, Fred. W.: A modification of the Devine operation of pyloric exclusion for duodenal ulcer, Am. J. Surg. **16**: 223-230, 1932.
33. Baritell, A.: Perforated gastroduodenal ulcer, Surgery **21**: 24-33, 1947.
34. Baronofsky, I.: Portal hypertension and the ulcer diathesis, Proc. Am. Fed. Clin. Res. **2**: 66, 1945.
35. Baronofsky, I., Lannin, B. G., Sanchez-Palomera, E., and Wangensteen, O. H.: Billroth I gastric resection: extent necessary to protect against histamine-provoked ulcer, Proc. Soc. Exper. Biol. & Med. **59**: 229-231, 1945.
36. Baronofsky, I., and Wangensteen, O. H.: The experimental production of erosion or ulcer (gastric and/or duodenal) by the intravenous injection of small amounts of fat in animals, Bull. Am. Coll. Surg. **30**: 59, 1945.
37. Baronofsky, I., and Wangensteen, O. H.: Erosion or ulcer (gastric and/or duodenal) experimentally produced through the agency of chronic arterial spasm invoked by the intramuscular implantation of epinephrine or pitressin in beeswax, Bull. Am. Coll. Surg. **30**: 59-60, 1945.
38. Bartels, R. N., and Dulin, J. W.: Gastric resection for peptic ulcer, Surgery **21**: 496-511, 1947.
39. Bastedo, W. A.: Determination of the need of surgery in peptic ulcer, with remarks on gastro-enterostomy, Am. J. M. Sci. **160**: 491-503, 1920.
40. Bauer, R., and Aron, E.: Role respectif de la suppression des secretions pancreatique et biliare, et de la resection duodenale dans la production des ulceres peptiques experimentaux, C. Rend. Soc. Biol. **113**: 1063-1065, 1933.
41. Baxter, S. G.: Nervous control of the pancreatic secretion in the rabbit, Am. J. Physiol. **96**: 349-355, 1931.
42. Baxter, S. G.: Influence of splanchnic nerves on gastric secretion, Proc. Soc. Exp. Biol. & Med. **29**: 511-512, 1932.
43. Baxter, S. G.: Role of the sympathetic nervous system in gastric secretion, Am. J. Dig. Dis. & Nutr. **1**: 40-42, 1934.
44. Bayliss, W. M., and Starling, E. H.: The mechanism of pancreatic secretion, J. Physiol. **28**: 325-353, 1902.
45. Beaver, M. G., and Mann, F. C.: The production of peptic ulcer after section of the gastric nerve, Ann. Surg. **94**: 1116-1118, 1931.
46. Beazell, J. M., and Ivy, A. C.: Chronic gastric ulcer following bilateral vagotomy in the rabbit and in the dog, Arch. Path. **22**: 213-219, 1936.

47. Benedict, E. B.: Jejunal ulcer—An analysis of 36 cases and study of the literature, Surg., Gyn., & Obst. **56**: 807-819, 1933.
48. Berg., A. A.: The radical operative cure of gastric and duodenal ulcer, S. Clin. N. America **8**: 1167-1191, 1928.
49. Berg, A. A.: The mortality and late results of subtotal gastrectomy for the radical cure of gastric and duodenal ulcer, Ann. Surg. **92**: 340-366, 1930.
50. Berg, B. N.: Peptic ulcers—comparative frequency after deprivation of bile and pancreatic juice, Arch. Surg. **28**: 1057-1061, 1934.
51. Berg, B. N.: Gastric ulcers produced experimentally by vascular ligation, Arch. Surg. **54**: 58-66, 1947.
52. Berg, B. N., and Jobling, J. W.: Biliary and hepatic factors in peptic ulcers, Arch. Surg. **20**: 997-1015, 1930.
53. Berg, B. N., Johnston, A., and Jobling, J. W.: Duodenal and gastric ulcers in dogs with biliary fistulas, Proc. Soc. Exp. Biol. & Med. **25**: 334-336, 1927.
54. Berg, B. N., and Zucker, T. F.: Comparative frequency of peptic ulcers after deprivation of bile and pancreatic juices, Proc. Soc. Expt. Biol. & Med. **30**: 330-332, 1932.
55. Berger, E. H.: The distribution of parietal cells in the stomach: A histotopographic study, Am. J. Anatomy **54**: 87-114, 1934.
56. Bergh, G. S.: Bile salts in the treatment of peptic ulcer, SURGERY **4**: 84-94, 1938.
57. Berk, J. E., Rehfuss, M. E., and Thomas, J. E.: The acidity of the ulcer-bearing area of the duodenum in normal persons, Am. J. Dig. Dis. **9**: 276-281, 1942.
58. Berk, J. E., Thomas, J. E., and Rehfuss, M. E.: The effect of gastric hypersecretion on the reaction and neutralizing ability of the contents of the first part of the duodenum in normal dogs, Am. J. Dig. Dis. **9**: 297-301, 1942.
59. Berk, J. E., Thomas, J. E., and Rehfuss, M. E.: The acid factor in duodenal ulcer as evaluated by the acidity and neutralizing ability in the duodenal bulb, Am. J. Dig. Dis. **9**: 331-375, 1942.
60. Best, C. H., and McHenry, E. W.: Histamine, Physiological Reviews, **11**: 371-477, 1931.
61. Best, R. R., and Orator, V.: The vagus nerve and its relation to peptic ulcer, Ann. Surg. **96**: 184-191, 1932.
62. Bickel, A.: Beobachtungen am Hunden mit exstirpiertem Duodenum, Klin. Wchnschr. **46**: 1201-1202, 1909.
63. Birgfeld, E.: Ueber das Ulcus pepticum jejuni nach Magen-resektion, Arch. f. klin. Chir. **137**: 568-582, 1925.
64. Blackford, J.: Massive gastric hemorrhage, Am. J. Dig. Dis. **6**: 638-641, 1939.
65. Blanck, E. E.: Peptic ulcer—An experimental study, Surg., Gyn., and Obst. **61**: 480-493, 1935.
66. Bloomfield, A. L.: The problem of gastric hyperacidity, Am. J. Dig. Dis. & Nutr. **6**: 700-702, 1940.
67. Bloomfield, A. L.: The indications for operation in cases of peptic ulcer from an internist's point of view, Surgery **17**: 692-695, 1945.
68. Bloomfield, A. L., and Keefer, C. S.: Clinical physiology of the stomach. Simultaneous quantitative observations on gastric secretory volume, acidity and motility, Arch. Int. Med. **38**: 145-157, 1926.
69. Boerema, I.: Gastroduodenal ulcer, a spastic disease, Ann. Surg. **127**: 413-416, 1948.
70. Bogoras, N.: Ueber Cholecystogastrostomie bei dem Magen-ulcus, Eine neue Operationsmethode zur Behandlung des Magenulcus, Arch. f. klin. Chir. **134**: 42-50, 1925.
71. Boldyreff, W.: The self-regulation of the acidity of the gastric contents and the real acidity of the gastric juice, Quart. J. Expt. Physiol. **8**: 1-12, 1914.
72. Bollman, J. L., and Mann, F. C.: Chronic duodenal ulcer in animals with Eck fistulas on certain diets, Arch. Path. **4**: 492, 1927.
73. Bollman, J. L., and Mann, F. C.: Peptic ulcer in experimental obstructive jaundice, Arch. Surg. **24**: 126-136, 1932.
74. Bolton, C.: Croonian lectures on the interpretation of gastric symptoms, Lancet **1**: 1263-1275, 1928.
75. Bolton, C., and Goodhart, C. W.: Duodenal regurgitation into the stomach during gastric digestion, Lancet **1**: 420-425, 1922.
76. Bolton, C., and Goodhart, C. W.: The mucus factor in the automatic regulation of the acidity of the gastric contents, J. Physiol. **77**: 287-309, 1933.
77. Bolton, C., and Salmond, R. W. A.: Antiperistalsis of the duodenum and its relation to pyloric regurgitation, Lancet **212**: 1230-1232, 1927.
78. Braun, H.: Ueber die Gastroenterostomie und gleichzeitige Enteroanastomose, Centralbl. f. Chir. **19**: 102, 1892.
79. Bruusgaard, C.: The operative treatment of chronic gastric and duodenal ulcer, Surgery **23**: 161-166, 1948.
80. Buchner, F., and Molloy, P. J.: Das echte peptische Geschwür der Ratte, Klin. Wchnschr. **6**: 2193-2194, 1927.

81. Burget, G. E., and Steinberg, M. E.: Studies on the physiology of gastroenterostomy I. The regurgitation of intestinal contents in normal dogs and dogs with posterior gastroenterostomy, Am. J. Physiol. **60**: 308-311, 1922.
82. Burkle-de-la-Camp, H.: Zur Pathologie und Chirurgie der peptischen Schadigungen des Magen-Darm kanals, Deutsche Ztschr. f. Chir. **220**: 31-88, 1929.
83. Cannon, W. B.: The acid control of the pylorus, Am. J. Physiol. **20**: 283, 1907.
84. Cannon, W. B., and Blake, J. B.: Gastroenterostomy and pyloroplasty—an experimental study by means of the Roentgen rays, Ann. Surg. **41**: 686-711, 1905.
85. Carlson, A. J.: The secretion of gastric juice in health and disease, Physiol. Rev. 3: 1-40, 1923.
86. Case, J. T.: Gastric and duodenal roentgen-ray findings after operation, J. A. M. A. **85**: 1385-1389, 1925.
87. Cheney, G.: Gastric acidity in chicks with experimental gastric ulcers, Am. J. Dig. Dis. **5**: 104-107, 1938.
88. Chlumsky, V.: Weitere Erfahrungen ueber die Gastroenterostomie, Beit. z. klin. Chir. **27**: 281-331, 1900.
89. Church, R. E., and Hinton, J. W.: The results of gastroenterostomy in gastric and duodenal ulcers—Report of 106 cases followed for an average of 7.1 years post-operatively, SURGERY **7**: 647-656, 1940.
90. Church, R. E., and Hinton, J. W.: Follow-up results in subtotal gastric resection for ulcer, Am. J. Dig. Dis. **9**: 317-321, 1942.
91. Code, C. F., and Varco, R. L.: Chronic histamine action, Proc. Soc. Exper. Biol. & Med. **44**: 475-477, 1940.
92. Code, C. F., and Varco, R. L.: Prolonged action of histamine, Am. J. Physiol. **137**: 225-233, 1942.
93. Comfort, M. W.: Acidity of the duodenal contents in health and disease—a review of clinical investigations, Gastroenterology **4**: 135-146, 1945.
94. Connell, F. G.: Fundusectomy—A new principle in the treatment of gastric and duodenal ulcer, Surg., Gynec., & Obst. **49**: 696-701, 1929.
95. Connell, F. G.: Partial gastrectomy in treatment of peptic ulcer, Surgery 3: 696-702, 1930.
96. Conneli, F. G.: Fundusectomy—experimental, Surg., Gynec., & Obst. **53**: 750-752, 1931.
97. Connell, F. G.: Resection of the fundus of the stomach for peptic ulcer, Ann. Surg. **96**: 200-203, 1932.
98. Counseller, U. S., Waugh, J. M., and Clagett, O. T.: Report of surgery of the stomach and duodenum for 1943, Proc. Staff Meet. Mayo Clinic **19**: 586-590, 1944.
99. Crandell, W. B., Boehm, W. E., and Mulholland, J. H.: Effects of supra-diaphragmatic section of the vagus nerves in man, Arch. Surg. **55**: 343-348, 1947.
100. Crile, G. W.: Recurrent hyperthyroidism, neurocirculatory asthenia and peptic ulcer, Treatment by operations on the suprarenal sympathetic system, J. A. M. A. **97**: 1616-1618, 1931.
101. Crile, G.: Peptic ulcer, South. Surg. **2**: 273-280, 1933.
102. Cushing, H.: Peptic ulcers and the interbrain, Surg., Gyn., & Obst. **55**: 1-34, 1932.
103. Custer, M. D., Butt, H. R., and Waugh, J. M.: The so-called dumping syndrome after subtotal gastrectomy in a clinical study, Ann. Surg. **123**: 410-418, 1946.
104. Cutler, E. C., and Zollinger, R.: Surgery of the stomach and duodenum—Procedures for peptic ulcer and gastric cancer, Surg., Gynec., & Obst. **67**: 318-332, 1938.
105. Day, J. J., and Webster, D. R.: The auto-regulation of the gastric secretion, Am. J. Dig. Dis. & Nutr. **2**: 527-531, 1935.
106. Deaver, J. B., and Reimann, S. P.: Subtotal gastrectomy, J. A. M. A. **85**: 1619-1625, 1925.
107. DeBakey, M. E.: Peptic ulceration—The relative protective value of the alkaline duodenal juices, Arch. Surg. **34**: 230-267, 1937.
108. DeBakey, M.: The physiology of peptic ulcer, SURGERY **2**: 653-674, 1937.
109. Denk, W.: Studien ueber die Atiologie und Prophylaxe des postoperativen jejunal Geschwüres, Arch. f. klin. Chir. **116**: 1-52, 1921.
110. De Takats, G.: The perverted physiology of the stomach after gastric operations, Am. J. M. Sci. **172**: 45-51, 1926.
111. De Takats, G.: The surgery of gastric and duodenal ulcers—Experience of the first surgical clinic, University of Budapest, Ann. Surg. **83**: 217-221, 1926.
112. De Takats, G., and Mann, F. C.: The effect on the jejunal mucosa of transplantation to the lesser curvature of the stomach, Ann. Surg. **85**: 698-703, 1927.
113. Devine, H. B.: Basic principles and supreme difficulties in gastric surgery, Surg., Gyn., & Obst., **40**: 1-16, 1925.
114. Dodds, E. C., Noble, R. L., and Smith, E. R.: A gastric lesion produced by an extract of the pituitary gland, Lancet **2**: 918-919, 1934.
115. Dott, D. M., and Lim, R. K. S.: Experimental jejunal ulcer, Quart. J. Exper. Physiol. Supp. XI **13**: 109-110, 1923.

116. Dolinski, I. L.: Influence of acids on the secretion of the pancreatic gland, Thesis, St. Petersburg, 1894—Quoted by Babkin (26).
117. Dragstedt, L. R.: Contributions to the physiology of the stomach. XXXVIII. Gastric juice in duodenal and gastric ulcers, J. A. M. A. **68**: 330-333, 1917.
118. Dragstedt, L. R.: Some physiologic principles involved in the surgical treatment of gastric and duodenal ulcer, Ann. Surg. **102**: 563-575, 1935.
119. Dragstedt, L. R.: Pathogenesis of gastro-duodenal ulcer, Arch. Surg. **44**: 438, 1942.
120. Dragstedt, L. R.: Some physiologic problems in surgery of the pancreas, Ann. Surg. **118**: 576-589, 1943.
120a. Dragstedt, L. R.: Vagotomy for gastroduodenal ulcer, Ann. Surg. **122**: 973-989, 1945.
121. Dragstedt, L. R., and Ellis, J. C.: The fatal effect of the total loss of gastric juice, Am. J. Physiol. **93**: 407-416, 1930.
121a. Dragstedt, L. R., Harper, P. U., Tovee, E. B., and Woodward, E. R.: Section of the vagus nerves to the stomach in the treatment of peptic ulcer, Ann. Surg. **126**: 687-699, 1947.
122. Dragstedt, L. R., and Owens, F. M.: Supradiaphragmatic section of the vagus nerves in treatment of duodenal ulcer, Proc. Soc. Exper. Biol. & Med. **53**: 152-154, 1943.
123. Dragstedt, L. R., Palmer, W. L., Schafer, P. W., and Hodges, P. C.: Supra-diaphragmatic section of the vagus nerves in the treatment of duodenal and gastric ulcers, Gastroenterology 3: 450-462, 1944.
124. Dragstedt, L. R., and Schafer, P. W.: Removal of the vagus innervation of the stomach in gastro-duodenal ulcer, SURGERY **17**: 742-749, 1945.
125. Dragstedt, L. R., and Vaughan, A. M.: Gastric ulcer studies, Arch. Surg. **8**: 791-810, 1924.
126. Driver, R. L., and Carmichael, E. B.: The effect of bile salts on the experimental production of ulcers in dogs, Am. J. Dig. Dis. **12**: 378-379, 1945.
127. Driver, R. L., Chappell, R. H., and Carmichael, E. B.: Effect of concentration of pepsin and the differential susceptibility of jejunal segments in experimental jejunal ulcers in the dog, Am. J. Dig. Dis. **12**: 166-167, 1945.
128. Driver, R. L., Chappell, R. H., and Carmichael, E. B.: Effect of hydrostatic pressure on the experimental production of ulcers, Am. J. Dig. Dis. **12**: 168-169, 1945.
129. Drury, D. R., McMaster, P. D., and Rous, P.: Observations on some causes of gallstone formation: III. The relation of the reaction of the bile to experimental cholelithiasis, J. Exp. Med. **39**: 403-423, 1924.
130. Durante, L.: The trophic element in the origin of gastric ulcer, Surg., Gyn., & Obst. **22**: 399-406, 1916.
131. Edkins, J. S.: The chemical mechanism of gastric secretion, J. Physiol. **34**: 133-144, 1906.
132. Edkins, J. S., and Tweedy, M.: The natural channels of absorption evoking the chemical mechanism of gastric secretion, J. Physiol. **38**: 263-267, 1908.
133. Elman, R.: Spontaneous peptic ulcers of the duodenum following the total loss of pancreatic juice, J. Clin. Investigation **10**: 183, 1931.
134. Elman, R.: Probable influence of pancreatic juice in the regulation of gastric acidity, Arch. Surg. **16**: 1256-1265, 1928.
135. Elman, R.: The behavior of gastric acidity in duodenal ulcer and pyloric obstruction before and after gastroenterostomy, Surg., Gyn., and Obst. **49**: 34-42, 1929.
136. Elman, R., and Eckert, C. T.: Neutralization of gastric acidity following pyloric closure, Proc. Soc. Exper. Biol. & Med. **30**: 1343-1344, 1933.
137. Elman, R., and Hartmann, A. F.: Spontaneous peptic ulcers of duodenum after continued loss of total pancreatic juice, Arch. Surg. **23**: 1030-1040, 1931.
138. Elman, R., and MacLeod, J. W.: Studies on the neutralization of gastric acidity: Ewald test meal and X-ray (barium meal) studies in patients with duodenal ulcer, gastro-jejunostomy and gastric resection, Am. J. Dig. Dis. & Nutr. **2**: 21-26, 1935.
139. Elman, R., and McCaughan, J. M.: On the collection of the entire external secretion of the pancreas under sterile conditions and the fatal effect of total loss of pancreatic juice, J. Exper. Med. **45**: 561-570, 1927.
140. Elman, R., and Rowlette, A. P.: The role of the pyloric sphincter in the behavior of gastric acidity, Arch. Surg. **22**: 426-437, 1931.
141. Emery, E. S., and Monroe, R. T.: Peptic ulcer—a study of 556 cases, Arch. Int. Med. **43**: 846-873, 1929.
142. Enderlen, E., and Zuckschwerdt, C.: Die Erregung der Magen—Saftsekretion nach Resektion des Antrum-Pylorusteils des Magens, Deutsche Ztschr. f. Chir. **232**: 290, 1931.
143. Eustermann, G. B.: Recurrent gastric ulcer and associated gastrojejunal ulcer in presence of constant gastric anacidity, M. Clin. North America **11**: 1371-1376, 1928.
144. Evert, J. A., Black, B. M., and Dockerty, M. B.: Primary non-specific ulcers of the small intestine, SURGERY **23**: 185-200, 1948.

145. Exalto, J.: Ulcus jejuni, nach Gastro-enterostomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **23**: 13, 1911.
146. Fauley, G. B., and Ivy, A. C.: Experimental jejunal ulcer, Proc. Soc. Exp. Biol. & Med. **27**: 182-483, 1929.
147. Fauley, G. B., and Ivy, A. C.: Experimental gastric ulcer—the effect of the consistency of the diet on healing, Arch. Int. Med. **46**: 524-532, 1930.
148. Fauley, G. B., and Ivy, A. C.: The prevention of post-operative jejunal ulcers by diet and fundusectomy, Surg., Gyn., & Obst. **63**: 717-723, 1936.
149. Fauley, G. B., and Ivy, A. C.: The factor of spasm in the etiology of jejunal ulcer, Am. J. Dig. Dis. & Nutr. **4**: 160-161, 1937.
150. Fauley, G. B., Strauss, H. A., and Ivy, A. C.: Studies on the effects of subtotal gastric resection in the dog, Am. J. Surg. **17**: 427-433, 1932.
151. Ferguson, A N.: A cytological study of the regeneration of gastric glands following the experimental removal of large areas of mucosa, Am. J. Anat. **42**: 403-435, 1928.
152. Finney, J. M. T.: The development of surgery of the stomach, Ann. Surg. **90**: 829-842, 1929.
153. Finney, J. M. T., and Hanrahan, E. M.: The surgical treatment of duodenal ulcer: end-results over a 25 year period, Ann. Surg. **90**: 904-917, 1929.
154. Finsterer, H.: Surgical treatment of acute profuse gastric hemorrhage, Surg., Gyn., & Obst. **69**: 291-298, 1939.
155. Finsterer, H., and Cunha, F.: The surgical treatment of duodenal ulcer, Surg., Gyn., & Obst. **52**: 1099-1114, 1931.
156. Flood, C. A., and Howes, E. L.: Experimental study on the effect of histamine on the healing of gastric defects—artificial gastric ulcer, Surg., Gyn., & Obst. **58**: 136-144, 1934.
157. Flood, C. A., and Mullins, C. R.: Experimental peptic ulcer—The effect of surgical duodenal drainage upon dogs and the value of histidine in preventing ulcer, Am. J. Dig. Dis. & Nutr. **3**: 249-255, 1936.
158. Florey, H. W., Jennings, M. A., Jennings, D. A., and O'Connor, R. C.: The reactions of the intestine of the pig to gastric juice, J. Path. & Bact. **49**: 105-123, 1939.
158a. Fogelman, M. J., Grossman, M. I., and Ivy, A. C.: Further studies on the effect of continuous intragastric infusion of acid and pepsin in dogs, SURGERY **25**: 60-67, 1949.
159. Fogelson, S. J.: The treatment of peptic ulcer with gastric mucin, J. A. M. A. **96**: 673-675, 1931.
160. Friedenwald, J.: A clinical study of a thousand cases of ulcer of the stomach and duodenum, Tr. A. Am. Physicians **27**: 280-295, 1912.
161. Friedenwald, J., and Feldman, M.: Experimental studies on the effect of secretion of the vagus nerve on gastric secretion, Arch. Int. Med. **49**: 234-240, 1932.
162. Friedenwald, J., Feldman, M., and Morrison, M.: The effect of acids and other substances in the production of acute gastric ulcers, J. Exp. Med. **57**: 203-213, 1933.
163. Friedman, G. A.: The experimental production of lesions, erosions and acute ulcers in rabbits, by repeated injections of pilocarpine and adrenaline, J. Med. Research **38**: 449-463, 1918.
164. Friedman, J. C., and Hamburger, W. W.: Experimental chronic gastric ulcer, J. A. M. A. **63**: 381-384, 1914.
165. Friesen, S. R., Baronofsky, I. D., and Wangensteen, O. H.: Benadryl fails to protect against the histamine-provoked ulcer, Proc. Soc. Exp. Biol. & Med. **63**: 23-25, 1946.
166. Friesen, S. R., State, D., Jasper, D. E., Finn, M., and Wangensteen, O. H.: Production of allergic gastric and duodenal edema which predisposes to the histamine-provoked ulcer in dogs, SURGERY **23**: 167-177, 1948.
167. Gage, M., Ochsner, A., and Hosoi, K.: Relationship of gastric acidity to peptic ulceration. I. Effect of hydrochloric acid, of histamine and of deviation of bile, Arch. Surg. **32**: 1019-1048, 1936.
168. Gallagher, W. J.: Acute traumatic ulcers of the small intestine. Observations on the effects of application of clamps on the gastrointestinal tract: an experimental study, Arch. Surg. **15**: 689-711, 1927.
169. Gallagher, W. J.: Effects of injections of acid and trauma on jejunal transplants to the stomach, Arch. Surg. **17**: 279-288, 1928.
170. Gallagher, W. J.: Effect of injections of hydrochloric acid on the gastric and duodenal mucosae, Arch. Surg. **17**: 613-626, 1928.
171. Gallagher, W. J., and Palmer, W. L.: Experimental jejunal ulcer; Relative importance of mechanical and chemical factors, Proc. Soc. Exp. Biol. & Med. **30**: 468-473, 1932.
172. Gatewood, D.: Immediate mortality and late results of operations for peptic ulcer, Ann. Surg. **92**: 554-557, 1930.
173. Gavin, G., McHenry, E. W., and Wilson, M. J.: Histamine in canine gastric tissues, J. Physiol. **79**: 234-238, 1933.
173a. Gaviser, D.: Clinical investigation and evaluation of 416 consecutively operated cases of peptic ulcer, Bull. Staff Meeting Univ. of Minn. **19**: 81-110, 1947.

174. Gentile, A.: Cholecystogastrostomy and hepatitis—an experimental study, Arch. Surg. **30**: 449-475, 1935.
175. Gilman, A., and Cowgill, G. R.: Effect of histamine on the secretion of gastric pepsin, Proc. Soc. Exper. Biol. & Med. **28**: 194-196, 1930.
176. Ginzburg, L., and Mage, S.: Failures following gastroenterostomy for gastro-duodenal ulcer, Surg., Gyn., & Obst. **67**: 788-795, 1938.
177. Goldberg, S. M.: A method of producing peptic ulcer experimentally, Ann. Surg. **96**: 155-156, 1932.
178. Graham, R. R.: Technical surgical procedures for gastric and duodenal ulcer, Surg., Gyn., & Obst. **66**: 269-287, 1938.
179. Graham, R. R.: The surgeon's problem in duodenal ulcer, Am. J. Surg. **40**: 102-117, 1938.
180. Graham, R. R., and Lewis, F. I.: Jejunal ulcer, J. A. M. A. **104**: 386-390, 1935.
181. Graham, R. R., and Tovee, M. L.: The treatment of perforated duodenal ulcers, SURGERY **17**: 704-711, 1945.
182. Graves, A. M.: Combined and separate effects of bile, pancreatic secretion and trauma in experimental peptic ulcer, Arch. Surg. **30**: 833-853, 1935.
183. Gray, J. S., Bradley, W. R., and Ivy, A. C.: On the preparation and biological assay of enterogastrone, Am. J. Physiol. **118**: 463-476, 1937.
184. Gray, J. S., Wieczorowski, E., and Ivy, A. C.: Inhibition of gastric secretion in man with urogastrone, Am. J. Dig. Dis. **7**: 513-515, 1940.
185. Greengard, H., Atkinson, A. J., Grossman, M. I., and Ivy, A. C.: The effectiveness of parenterally administered enterogastrone in the prophylaxis of recurrences of experimental and clinical peptic ulcer, Gastroenterology **7**: 625-649, 1946.
186. Greengard, H., and Ivy, A. C.: The isolation of secretin, Am. J. Physiol. **124**: 427-434, 1938.
187. Greengard, H., Stein, I. F., and Ivy, A. C.: Certain quantitative aspects of the pancreatic response to secretin, Am. J. Physiol. **132**: 305-309, 1941.
188. Gregory, R. A., and Ivy, A. C.: The humoral stimulation of gastric secretion, Quart. J. Exp. Physiol. **31**: 111-128, 1941.
189. Grey, E. G.: An experimental study of the effect of cholecystogastrostomy on gastric acidity, J. Exp. Med. **23**: 15-24, 1916.
190. Grey, E. G.: The diversion of the pancreatic juice from the duodenum into the stomach. Its effects upon the level of gastric acidity and upon the pancreas, J. Exper. Med. **26**: 825-840, 1917.
191. Grey, E. G.: Duodenectomy—Its effect upon the life of an animal, Surg., Gynec., & Obst. **28**: 36-42, 1919.
192. Griffiths, W. J.: The duodenum and the automatic control of gastric acidity, J. Physiol. **87**: 34-40, 1936.
193. Grimson, K. S., Baylin, G. J., Taylor, H. M., Hesser, F. H., and Rundles, R. W.: Clinical evaluation of complications observed after transthoracic vagotomy, Arch. Surg. **55**: 175-179, 1947.
194. Grindlay, J. H.: Studies on secretion of acid following procedures on the distal end of the stomach, Am. J. Dig. Dis. **8**: 82-85, 1941.
195. Gross, W.: Arch. F. Verdauungs Krankheiten **12**: 507, 1906, Quoted by Keeton and Koch (263).
196. Grossman, A.: Post-operative jejunal ulcer—A study of 23 cases operated upon at the Presbyterian Hospital, New York, Ann. Surg. **108**: 105-123, 1938.
197. Grossman, M. I., Dutton, D. F., and Ivy, A. C.: An attempt to confirm the alleged inhibitory effect on gastric secretion of jejunal pedicle grafts in the wall of the stomach, SURGERY **17**: 685-692, 1945.
198. Grossman, M. I., Dutton, D. F., and Ivy, A. C.: An attempt to prevent histamine-induced ulcers in dogs by the administration of enterogastrone concentrates, Gastroenterology **6**: 145-146, 1946.
199. Haberer, H.: Zur radical Operation des Ulcus pepticum jejuni post-operativum, Arch. f. klin. Chir. **101**: 668-696, 1913.
200. Haberer, H.: Anwendungsbreite und Vorteil der Magenresektion nach Billroth I, Arch. f. klin. Chir. **114**: 127-171, 1920.
201. Haberer, H.: Die Bedeutung des Pylorus für das Zustandekommen des post-operativen Jejunal ulcus, Arch. f. klin. Chir. **117**: 50-67, 1921.
202. Halperin, G.: The pathogenesis of the gastro-duodenal ulcer, Surg., Gynec., & Obst. **43**: 173-180, 1926.
203. Harde, E.: Lesions gastriques de souris apres injections repetees d'histamine, C. Rend. Soc. Biol. **109**: 1326-1327, 1932.
204. Hardt, L. L. J.: The secretion of gastric juice in cases of gastric and duodenal ulcer, Am. J. Physiol. **40**: 314-332, 1916.
205. Harkins, H. N.: Acute ulcer of the duodenum (Curling's ulcer) as a complication of burns; Relation to sepsis, SURGERY **3**: 608-641, 1938.

206. Harkins, H. N., and Hooker, D. W.: Vagotomy for peptic ulcer—experimental and clinical studies, SURGERY **22**: 239-245, 1948.
207. Harper, F. R.: Development of experimental peptic ulcer, changes in acidity and treatment, Proc. Staff Meet. Mayo Clinic **7**: 318-323, 1932.
208. Harper, F. R.: Development and treatment of peptic ulcer—an experimental study, Arch. Surg. **30**: 394-404, 1935.
209. Hartzell, J. B.: The effect of section of the vagus nerves on gastric acidity, Am. J. Physiol. **91**: 161-171, 1929.
210. Harvey, B. C. H.: A study of the structure of the gastric glands of the dog and of the changes which they undergo after gastroenterostomy and occlusion of the pylorus, Am. J. Anat. **6**: 207-244, 1906.
211. Hawkins, W. B., and Whipple, G. H.: Bile fistulas and related abnormalities, J. Exp. Med. **62**: 599-620, 1935.
212. Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H.: The experimental production of gastric and duodenal ulcers in laboratory animals by the intramuscular injection of histamine in beeswax, Surg., Gyn., & Obst. **75**: 170-182, 1942.
213. Heintz, E. L., and Welker, W. H.: Acidity curves in gastric, duodenal and mixed ulcers, Ann. Clin. Med. **3**: 371-379, 1925.
214. Held, I. W., and Goldbloom, A. A.: Pathogenesis of peptic ulcer, M. Clin. North America **14**: 319-364, 1930.
215. Helmer, O. M.: The relation of the secretion of mucus to the acidity of the gastric juice, Am. J. Physiol. **110**: 28-36, 1934.
216. Heuer, G. J., and Holman, C.: The effect on gastric acidity of gastroenterostomy and gastric resection for peptic ulcer, Ann. Surg. **118**: 551-557, 1943.
217. Heuer, G. J., Holman, C., and Cooper, W. A.: Treatment of peptic ulcer, Lippincott, Philadelphia, 1944.
218. Hinton, J. W.: Sequelae of peptic ulcer following medical and surgical treatment, Arch. Surg. **31**: 137-150, 1935.
219. Hinton, J. W.: The surgical treatment for massive hemorrhage in peptic ulcer, S. Clin. North America **18**: 539, 1938.
220. Hoerner, M. T.: The effect of exclusion of the pancreatic juice from the duodenum—an experimental study, Proc. Staff Meet. Mayo Clinic **9**: 473-476, 1934.
221. Hoerner, M. T.: The effect of exclusion of the pancreatic secretion by evulsion of the pancreatic ducts on the reaction of the duodenal content, Am. J. Dig. Dis. & Nutr. **2**: 295-297, 1935.
222. Hoerner, M. T.: The effect of exclusion of the pancreatic secretion by a pancreatic fistula on the reaction of the gastric, duodenal and jejunal contents, Am. J. Dig. Dis. & Nutr. **2**: 298-300, 1935.
223. Hoerner, M. T.: The buffer capacity of the pancreatic juice, Am. J. Dig. Dis. & Nutr. **2**: 300-302, 1935.
224. Hoerner, M. T.: Peptic ulcer following loss of pancreatic secretion through a fistula: An experimental study, Am. J. Dig. Dis. & Nutr. **2**: 302-305, 1935.
225. Hoffmann, A.: Experimental gastric and duodenal inflammation and ulcer produced with a specific organism fulfilling Koch's postulates, Am. J. M. Sci. **170**: 212-220, 1925.
226. Hollander, F.: The components of the gastric secretion, Am. J. Dig. Dis. & Nutr. **3**: 651-655, 1937.
227. Hollander, F.: Factors which reduce gastric acidity, Am. J. Dig. Dis. **5**: 369-372, 1938.
228. Hollander, F.: The insulin test for the presence of intact nerve fibers after vagal operations for peptic ulcer, Gastroenterology **7**: 607-614, 1946.
229. Holman, C., and McSwain, B. A.: Gastric acidity following gastric resection, SURGERY **13**: 916-923, 1943.
230. Holman, C., and Sandusky, W. R.: Gastric acidity after gastroenterostomy, Am. J. M. Sci. **195**: 220-230, 1938.
231. Hooper, C. W., and Whipple, G. H.: Bile pigment metabolism—I. Bile pigment output and diet studies, Am. J. Physiol. **40**: 332-347, 1916.
232. Horsley, J. S.: The immediate mortality and late results of operations for gastric and duodenal ulcers, Ann. Surg. **92**: 545-553, 1930.
233. Hughson, W.: Relation of the pylorus to duration of experimental gastric ulcer, Arch. Surg. **15**: 66-74, 1927.
234. Hunt, V. C.: Principles which govern the extent of gastric resection for duodenal ulcer, Surg., Gyn., & Obst. **73**: 676-680, 1941.
235. Hurst, A. F.: The sphincters of the alimentary canal and their clinical significance, Brit. M. J. **1**: 145-151, 1925.
236. Hurst, A. F., and Stewart, M. J.: Jejunal and gastro-jejunal ulcers, Lancet. **2**: 742-748, 1928.
237. Hutchison, R.: Disappointments after gastroenterostomy, Brit. M. J. **1**: 535-536, 1919.
238. Imes, P. R.: The reaction of the content of the isolated duodenum, Am. J. Dig. Dis. & Nutr. **2**: 285-288, 1935.

239. Ivy, A. C.: Studies on the secretion of the pyloric end of the stomach, Am. J. Physiol. **49:** 142-143, 1919.
240. Ivy, A. C.: Studies on gastric and duodenal ulcer, J. A. M. A. **75:** 1540-1542, 1920.
241. Ivy, A. C.: Contributions to the physiology of the stomach—LII. Studies on gastric ulcer, Arch. Int. Med. **25:** 6-31, 1920.
242. Ivy, A. C.: A hormone mechanism for gall-bladder contraction and evacuation, Am. J. Surg. **7:** 455-459, 1929.
243. Ivy, A. C.: The mechanisms of gastric secretion, SURGERY **10:** 861-878, 1941.
244. Ivy, A. C.: The prevention of recurrence of "peptic ulcer": An experimental study, Gastroenterology 3: 443-449, 1944.
245. Ivy, A. C.: The problem of peptic ulcer, J. A. M. A. **132:** 1053-1059, 1946.
246. Ivy, A. C., Droegemueller, E. H., and Meyer, J. L.: Effect of experimental pyloric stenosis on gastric secretion, Arch. Int. Med. **40:** 434-445, 1927.
247. Ivy, A. C., and Farrell, J. I.: Contributions to the physiology of gastric secretion—VIII. The proof of a humoral mechanism—A new procedure for the study of gastric physiology, Am. J. Physiol. **74:** 639-649, 1925.
248. Ivy, A. C., and Fauley, G. B.: Factors concerned in determining the chronicity of ulcers in the stomach and upper intestine. 1. The susceptibility of jejunum to ulcer formation. 2. Effect of diet on healing of acute gastric ulcer, Am. J. Surg. **11:** 531-543, 1931.
249. Ivy, A. C., Lim, R. K. S., and McCarthy, J. E.: Contributions to the physiology of gastric secretion—II. The intestinal phase of gastric secretion, Quart. J. Exp. Physiol. **15:** 55-68, 1925.
250. Ivy, A. C., Lim, R. K. S., and McCarthy, J. E.: Contributions to the physiology of gastric secretion—III. An attempt to prove that a humoral mechanism is concerned in gastric secretion by blood transfusion and cross circulation, Am. J. Physiol. **74:** 616-638, 1925.
251. Ivy, A. C., and McIlvain, G. U.: The excitation of gastric secretion by application of substances to the duodenal and jejunal mucosa, Am. J. Physiol. **63:** 418-419, 1923.
252. Ivy, A. C., and Oyama, Y.: Studies on the secretion of pars pylorica gastri, Am. J. Physiol. **57:** 51-60, 1921.
253. Ivy, A. C., Schrager, V. L., and Morgan, J. E.: Spontaneous duodenal ulcers in dogs with chronic mild icterus and hepatitis, Proc. Soc. Exp. Biol. & Med. **30:** 698-700, 1932.
254. Ivy, A. C., and Whitlow, J. E.: The gastrin theory put to physiological test, Am. J. Physiol. **60:** 578-588, 1922.
255. Jenkins, H. P., and Palmer, W. L.: Studies on experimental jejunal ulcer, Proc. Soc. Exp. Biol. & Med. **28:** 935-936, 1931.
256. Jones, K. K.: A comparison of the buffer value of bile and pancreatic juice secreted simultaneously, Proc. Soc. Exp. Biol. & Med. **28:** 567-568, 1931.
257. Judd, E. S.: Jejunal ulcer, Surg., Gyn., & Obst. **33:** 120-126, 1921.
258. Judd, E. S., Jr.: Experimental production of peptic ulcers with caffein, Bull. Am. Coll. Surgeons **28:** 46-47, 1943.
259. Judd, E. S., and Hazeltine, M. E.: The results of operations for excision of ulcer of the duodenum, Ann. Surg. **92:** 563-573, 1930.
260. Judd, E. S., and Hoerner, M. T.: Jejunal ulcer, Ann. Surg. **102:** 1003-1018, 1935.
261. Kapsinow, R.: The experimental production of duodenal ulcer by exclusion of bile from the intestine. Ann. Surg. **83:** 614-617, 1926.
262. Katzenstein, M.: Beitrag zur Entstehung des Magengeschwürs. Arch. f. klin. Chir. **100:** 939-961, 1913.
263. Keeton, R. W., and Koch, F. C.: The distribution of gastrin in the body, Am. J. Physiol. **37:** 481-504, 1915.
264. Kehrer, J. K. W.: Ueber die Ursache des runden Magengeschwüres, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27:** 679-693, 1914.
265. Keller, A. D., Hare, W. K., and D'Amour, M. C.: Ulceration in digestive tract following experimental lesions in brainstem, Proc. Soc. Exp. Biol. & Med. **30:** 772-775, 1932.
266. Kennedy, C. S., and Reynolds, R. P.: Does anterior gastrojejunostomy predispose to development of jejunal ulcerations?—A study based upon ninety partial gastrectomies, Am. J. Surg. **72:** 36-39, 1946.
267. Kennedy, C. S., Reynolds, R. P., and Cantor, M. O.: A study of the gastric stoma after partial gastrectomy—An analysis of ninety gastric resections, SURGERY **22:** 41-47 1947.
268. Kennedy, C. S., Reynolds, R. P., and Cantor, M. O.: Demonstration at operation of sphincteric action at the true gastric stoma, Am. J. Surg. **74:** 808-810, 1947.
269. Keppich, J.: Ueber das Ulcus pepticum jejuni nach Pylorusauschaltung (erste Mitteilung einiger Tierversuche), Zentralbl. f. Chir. **48:** 118-122, 1921.
270. Kesavalu, A., and Mann, F. C.: The influence of duodenal contents on intragastric acidity, Surgery **14:** 578-587, 1943.

271. Kiefer, E. D.: Jejunal ulcers and recurrent hemorrhages after partial gastrectomy for peptic ulcer, J.A.M.A. **120:** 819-824, 1940.
272. Kim, M. S., and Ivy, A. C.: The prevention of experimental duodenal ulcer by feeding neutral gastric mucin, J.A.M.A. **97:** 1511-1513, 1931.
273. King, M. K.: Subtotal gastrectomy in the treatment of ulcer, Am. J. Surg. **71:** 350-354, 1946.
274. Klein, E.: Gastric secretion after partial gastrectomy, J.A.M.A. **89:** 1235-1239, 1927.
275. Klein, E.: Gastric secretion. II. Studies in a transplanted gastric pouch without Auerbach's plexus, Arch. Surg. **25:** 442-457, 1932.
276. Kogut, B., and Stein, E.: Gastroileostomy and gastro-ileac ulcer, Am. J. Surg. **33:** 263-269, 1936.
277. Kolouch, F.: A direct visual technique for studying chemical and other injury to exposed mucosal surfaces, Surgery **17:** 641-644, 1945.
278. Kolouch, F.: Rationale of the short afferent duodeno-jejunal loop in gastric resection for ulcer, Ph. D. Thesis—Univ. of Minnesota, Nov., 1946.
279. Kolouch, F.: The relationship between the volume of pancreatic secretion and the length of the afferent duodeno-jejunal loop in gastrectomized dogs, Bull. Am. Coll. Surgeons **32:** 240, 1947.
280. Kolouch, F.: Castellanos-Moreno, M., Dubus, A. T. S., Baronofsky, I., and Wangensteen, O. H.: Mechanism of stomal ulcer is related to length of afferent duodeno-jejunal loop, Proc. Soc. Exp. Biol. & Med. **58:** 275-280, 1945.
281. Kolouch, F., Bubus, A. T. S., and Wangensteen, O. H.: The pedicled jejunal transplant onto the gastric wall and evaluation of its effect upon gastric acidity and failure of such transplants to afford protection against ulcer provoked by histamine in beeswax, SURGERY **17:** 667-685, 1945.
282. Komarov, S. A.: Studies on gastrin: I. Methods of isolation of a specific gastric secretogogue from the pyloric mucous membrane and its chemical properties, Revue Canad. Biol. **1:** 191, 1942, II. Physiological properties of the specific gastric secretagogue from the pyloric mucous membrane, Revue Canad. Bull. **1:** 377, 1942.
283. Konjetzny, G. E.: The inflammatory basis of the development of typical ulcer of the stomach and duodenum, Internat. Abstr. Surg. **52:** 23-24, 1931.
284. Kosaka, T., and Lim, R. K. S.: Demonstration of the humoral agent in fat inhibition of gastric secretion, Proc. Soc. Exper. Biol. & Med. **27:** 890-891, 1930.
285. Lahey, F. H.: Diagnosis and management of gastrojejunal ulcer and gastrojejunocolic fistula, S. Clin. North America **20:** 767-780, 1940.
286. Lahey, F. H.: A simple useful anterior gastroenterostomy, Surg., Gyn., & Obst. **78:** 169-172, 1944.
287. Lahey, F. H.: Inflammatory lesions of the stomach and duodenum, J.A.M.A. **127:** 1030-1037, 1945.
288. Lahey, F. H., and Jordan, S. M.: Gastrojejunal ulcers and gastro-jejunocolic fistulae, Ann. Surg. **87:** 231-244, 1928.
289. Lahey, F. H., and Marshall, S. F.: The surgical treatment of peptic ulcer based upon one hundred and thirty subtotal gastrectomies for peptic ulcer, New England J. Med. **217:** 933-940, 1937
290. Lahey, F. H., and Marshall, S. F.: Technique of subtotal gastrectomy for ulcer, Surg., Gyn., & Obst. **69:** 498-507, 1939.
291. Lahey, F. H., and Marshall S. F.: The surgical management of some of the more complicated problems of peptic ulcer, Surg., Gyn., & Obst. **76:** 641-648, 1943.
292. Lahey, F. H., and Swinton, N. W.: Gastro-jejunal ulcer and gastro-jejunocolic fistula, Surg., Gyn., & Obst. **61:** 599-612, 1935.
293. Lake, N. C.: The later results of partial gastrectomy, Lancet **2:** 268-274, 1928.
294. Langeskiold, F.: Ueber die Widerstandsfähigkeit einiger lebender Gewebe gegen die Einwirkung eiweisspaltender Enzyme. Eine experimentelle Studie, Skandinav. Arch. f. Physiol. **31:** 1-74, 1914.
295. Lannin, B. G.: Experimental evaluation of a satisfactory operation for ulcer, Surgery **17:** 712-741, 1945.
296. Lannin, B. G., Hay, L. J., Judd, E. S., and Wangensteen, O. H.: Evaluation of a satisfactory operation for ulcer, Proc. Soc. Exp. Biol. & Med. **56:** 231-233, 1944.
297. Layne, J. A., and Bergh, G. S.: The effect of ligation of arteries of the stomach upon acid gastric secretion and upon the endoscopic appearance of the gastric mucosa in the dog, SURGERY **13:** 136-144, 1943.
298. LeVeen, H. H.: The effect of surgical interruption of the gastric blood flow upon gastric secretion and the prevention of experimental peptic ulcers, Surg., Gyn., & Obst. **86:** 164-168, 1948.
299. Lewis, E. B.: Acidity of gastric contents after excision of the antral mucosa, SURGERY **4:** 692-699, 1938.
300. Lewisohn, R.: The frequency of gastrojejunal ulcers, Surg., Gyn., & Obst. **40:** 70-76, 1925.

301. Lewisohn, R.: Gastric resection for duodenal ulcer, Surg., Gyn., & Obst. **80:** 355-360, 1945.
302. Lewisohn, R., and Ginzburg, L.: The relation of postoperative achlorhydria to the cure of gastric and duodenal ulcer, Surg., Gyn., & Obst. **44:** 344-354, 1927.
303. Li, T., and Freeman, S.: The frequency of "peptic" ulcers in protein-deficient dogs, Gastroenterology **6:** 140-144, 1946.
304. Light, R. U., Bishop, C. C., and Kendall, L. G.: The production of gastric lesions in rabbits by injection of small amounts of pilocarpine into the cerebrospinal fluid, J. Pharmacol. & Exper. Therap. **45:** 227-251, 1932.
305. Lillehei, C. W.: The influence of gastric denervation on the histamine provoked ulcer, Bull. Am. Coll. Surgeons **32:** 237, 1947.
306. Lim, R. K. S.: The question of a gastric hormone, Quart. J. Exper. Physiol. **13:** 78-103, 1922.
307. Lim, R. K. S., and Ammon, S. F.: The effects of portal and jugular injections of pyloric extracts on gastric secretion, Quart. J. Exper. Physiol. **13:** 115-129, 1922.
308. Lim, R. K. S., and Dott, N. M.: Observations on the isolated pyloric segment and on its secretion, Quart. J. Exper. Physiol. **13:** 159-176, 1923.
309. Lim, R. K. S., Matheson, A. R., and Schlapp, W.: Observations on the human gastro-duodenal secretions with special reference to the action of histamine, Quart. J. Exper. Physiol. **13:** 361-391, 1923.
310. Lindau, A., and Wulff, H.: The peptic genesis of gastric and duodenal ulcer especially in the light of ulcers in Meckel's diverticulum and the post-operative ulcers in the jejunum, Surg., Gyn., & Obst. **53:** 621-634, 1931.
311. Lium, R.: Peptic ulcer and diarrhea following the removal of the prevertebral ganglia in dogs, SURGERY **9:** 538-553, 1941.
312. Lord, J. W., Andrus, W. D., and Stefko, P.: Comparative effects of pedicle grafts from different levels of intestinal tract on pH of gastric mucosa, Proc. Soc. Exp. Biol. & Med. **52:** 100-101, 1943.
313. Lord, J. W., Andrus, W. D., and Stefko, P.: Effects of jejunal transplants on experimental production of peptic ulcers, Arch. Surg. **46:** 459-464, 1943.
314. MacCallum, W. G.: On the pathogenesis of chronic gastric ulcer, American Medicine **8:** 452-454, 1904.
315. MacLagan, N. F.: A statistical analysis of 389 fractional test meals with special reference to duodenal regurgitation, Quart. J. Med. **3:** 321-340, 1934.
316. MacLean, H., and Griffiths, W. J.: The automatic regulation of gastric acidity, J. Physiol. **66:** 356-370, 1928.
317. Mage, S.: Recurrent ulceration following subtotal gastrectomy in the treatment of gastroduodenal ulcer, Ann. Surg. **116:** 729-737, 1942.
318. Maier, H. C., and Grossman, A.: Relation of duodenal regurgitation to the development of jejunal ulcers, SURGERY **2:** 265-274, 1935.
319. Manhoff, L. J., and Poth, E. J.: The relation of pancreatic secretion to peptic ulcer formation—the effect of pancreatectomy and ligation of pancreatic ducts on the production of histamine induced ulcers in the dog, Bull. Am. Coll. Surgeons **32:** 236, 1947.
320. Mann, F. C.: A study of the gastric ulcers following removal of the adrenals, J. Exp. Med. **23:** 203-210, 1916.
321. Mann, F. C.: A further study of the gastric ulcers following adrenalectomy, J. Exp. Med. **24:** 329-332, 1916.
322. Mann, F. C.: The chemical and mechanical factors in experimentally produced peptic ulcer, S. Clin. North America **5:** 753-776, 1926.
323. Mann, F. C.: The experimentally produced peptic ulcer, Am. J. Surg. **7:** 453-454, 1929.
324. Mann, F. C.: Physiologic factors in relationship to peptic ulceration. Symposium on gastroenterology—Duke University, Oct. 12, 1947.
325. Mann, F. C., and Bollman, J. L.: The reaction of the content of the gastro-intestinal tract, J.A.M.A. **95:** 1722-1724, 1930.
326. Mann, F. C., and Bollman, J. L.: Experimentally produced peptic ulcers—development and treatment, J.A.M.A. **99:** 1576-1582, 1932.
327. Mann, F. C., and Bollman, J. L.: A symposium concerned with the duodenal factors in the neutralization of acid chyme, Am. J. Dig. Dis. & Nutr. **2:** 284-285, 1935.
328. Mann, F. C., and Kawamura, K.: Duodenectomy, Ann. Surg. **75:** 208-220, 1922.
329. Mann, F. C., and Williamson, C. S.: The experimental production of peptic ulcer, Ann. Surg. **77:** 409-422, 1923.
330. Marshall, S. F.: Recurrent ulcer resulting from inadequate gastric resection, Lahey Clin. Bull. **4:** 182-185, 1945.
331. Marshall, S. F., and Kiefer, E. D.: Partial gastrectomy for gastric or duodenal ulcer, J.A.M.A. **109:** 1341-1347, 1937.
332. Matthes, M.: Untersuchungen ueber die Pathogenese des Ulcus rotondum ventriculi und ueber den Einfluss von Verdauungsenzym auf lebendes und todtes Gewebe, Beitr. z. Path. Anat. u. z. all. Path. **13:** 309-364, 1893.

333. Matthews, W. B.: Production of intestinal ulcers by active gastric juice, Proc. Soc. Exp. Biol. & Med. **28:** 960-961, 1931.
334. Matthews, W. B., and Dragstedt, L. R.: The etiology of gastric and duodenal ulcer—experimental studies, Surg., Gyn., & Obst. **55:** 265-285, 1932.
335. Matzner, M. J., and Windwer, C.: Pepsin versus hydrochloric acid in the experimental production of gastric ulcer, Am. J. Dig. Dis. & Nutr. **4:** 180-183, 1937.
336. Mayo, W. J.: Gastrojejunal ulcers (Pseudojejunal ulcers), Surg., Gyn., & Obst. **10:** 227-229, 1910.
337. McCann, J. C.: Studies on the control of the acidity of the gastric juice, Am. J. Physiol. **89:** 483-496, 1929.
338. McCann, J. C.: Studies on the emptying of the stomach, Am. J. Physiol. **89:** 497-507, 1929.
339. McCann, J. C.: Experimental peptic ulcer, Arch. Surg. **19:** 600-659, 1929.
340. McCarthy, H. H.: The effect of vagotomy and partial gastrectomy on gastric acidity; effect of stimulation of the psychic phase in presence of tenth-normal hydrochloric acid in the stomach, Proc. Staff Meet. Mayo Clinic **21:** 142-150, 1946.
341. McClure, R. D., and Fallis, L. S.: Partial gastrectomy for peptic ulcer—a review of seventy-four operations, SURGERY **8:** 575-586, 1940.
342. McCrea, E. D., and McSwiney, B. A.: The effect of stimulation of the vagi on the pyloric region of the stomach, J. Physiol. **61:** 28-34, 1926.
343. McGee, L. C., and Hastings, A. B.: The carbon dioxide tension and acid base balance of jejunal secretions in man, J. Biol. Chem. **142:** 893-904, 1942.
344. McIlroy, P. T.: Experimental production of gastric ulcer, Proc. Soc. Exper. Biol. & Med. **25:** 268-269, 1927.
345. McMaster, Paul E.: Effects of diverting the gastric contents to the lower intestinal levels, Arch. Surg. **28:** 825-836, 1934.
346. McRoberts, J. W.: The reaction of the duodenal content after exclusion of bile from the duodenum, Am. J. Dig. Dis. & Nutr. **2:** 293-294, 1935.
347. Means, J. H.: Treatment of peptic ulcer—indications for surgery, Surg., Gyn., & Obst. **66:** 264-268, 1938.
348. Mecray, P. M., Barden, R. P., and Ravdin, I. S.: Nutritional edema: its effect on the gastric emptying time before and after operation, SURGERY **1:** 53-64, 1937.
349. Medoff, J., Neuwelt, F., Patedjl, J., and Necheles, H.: A study of the functions of the stomach following pyloric obstruction and gastroenterostomy, Am. J. Physiol. **133:** 386, 1941.
350. Meek, W. J., and Herren, R. C.: The effect of vagotomy on gastric emptying time, Am. J. Physiol. **109:** 221-231, 1934.
351. Mellanby, J.: The secretion of pancreatic juice, J. Physiol. **61:** 419-435, 1926.
352. Mellanby, J., and Huggett, A. S.: The relation of secretin formation to the entrance of acid chyme into the small intestine—the properties of secretin, J. Physiol, **61:** 122-130, 1926.
353. Merendino, K. A., Judd, E. S., Baronofsky, I., Litow, S., and Wangensteen, O. H.: Influence of caffeine on ulcer genesis, SURGERY **17:** 650-666, 1945.
354. Merendino, K. A., Lannin, B. G., Kolouch, F., Baronofsky, I., Litow, S. S., and Wangensteen, O. H.: Length of afferent duodenojejunal loop in gastric resection, a factor in stomal ulcer, Proc. Soc. Exp. Biol. & Med. **58:** 226-230, 1945.
355. Merendino, K. A., Litow, S. S., Armstrong, W. D., and Wangensteen, O. H.: The experimental production of erosions or ulcer (Gastric and/or duodenal) in animals by fracture or curettement of bone marrow, Bull. Am. Coll. Surgeons **30:** 58, 1945.
356. Merendino, K. A., Litow, S. S., and Wangensteen, O. H.: Failure of fracture or the curettement of the marrow of long bones in dogs or fracture in man to cause stimulation of gastric secretion, Bull. Am. Coll. Surgeons **30:** 58-59, 1945.
357. Merendino, K. A., Varco, R. L., Litow, S., Kolouch, F., Baronofsky, I., and Wangensteen, O. H.: Stomal ulcer attending complete intragastric regurgitation influenced by length of afferent duodeno-jejunal loop, Proc. Soc. Exp. Biol. & Med. **58:** 222-225, 1945.
358. Metz, M. H.: A gastric lesion produced by posterior pituitary extract, Texas State J. Med. **34:** 295-297, 1938.
359. Meulengracht, E.: The medical treatment of peptic ulcer and its complications, Brit. M. J. **2:** 321-324, 1939.
360. Meyer, J., Maskin, M., and Necheles, H.: Studies on constitution and ulcer—III. Gastric secretion in the healthy members of ulcer families, Am. J. Dig. Dis. & Nutr. **3:** 474-476, 1936.
361. Milanes, F.: The pathological physiology of the stomach following subtotal gastrectomy for gastro-duodenal ulcer, Am. J. Dig. Dis. & Nutr. **3:** 186-188, 1936.
362. Miller, G. G.: Report on 230 cases of subtotal gastric resection for peptic ulcer, SURGERY **12:** 383-392, 1942.

363. Miller, T. G., and Karr, W. G.: Intubation studies of the human small intestine. III. The influence of variations in the reaction and the motility of the stomach contents on the reaction and the motility of the intestinal contents, Am. J. Roentg. **35**: 300-305, 1936.
364. Miyagawa, Y.: The exact distribution of the gastric glands in man and in certain animals, J. Anat. **55**: 56-67, 1920.
365. Montgomery, A. H.: Gastro-jejunal ulcer—an experimental study, Arch. Surg. **6**: 136-150, 1923.
366. Moore, F. D.: Resection of the vagus nerves for ulcer—an interim evaluation—I. Operative technic and hospital management, Arch. Surg. **55**: 164-175, 1947.
367. Moore, F. D.: Current practices in the surgical treatment of ulcer, S. Clin. North America **27**: 1071-1087, 1947.
368. Moore, F. D., Chapman, W. P., Schulz, M. D., and Jones, C. M.: Transdiaphragmatic resection of the vagus nerves for peptic ulcer, New England J. Med. **234**: 241-251, 1946.
369. Morrison, S.: A modern conception of gastric secretory functions based upon recent investigations and newer interpretations, Am. J. Dig. Dis. **5**: 617-627, 1938.
370. Morton, C. B.: Observations on peptic ulcer—I. A method of producing chronic gastric ulcer, Ann. Surg. **85**: 207-221, 1927.
371. Morton, C. B.: Observations on peptic ulcer—II. A roentgenologic study of experimental chronic ulcer, Ann. Surg. **885**: 221-229, 1927.
372. Morton, C. B.: Observations on peptic ulcer—III. Healing of experimental peptic ulcer after gastroenterostomy, Ann. Surg. **85**: 229-236, 1927.
373. Morton, C. B.: Observations on peptic ulcer—IV. Patch transplants of jejunum in the stomach, Ann. Surg. **85**: 879-885, 1927.
374. Morton, C. B.: Observations on peptic ulcer—V. Findings in experimentally produced peptic ulcer: etiology and therapeutic considerations, Ann. Surg. **87**: 401-422, 1928.
375. Morton, C. B.: Observations on peptic ulcer—VI. Preliminary report of clinical experiments with gastroduodenal analysis, Am. J. Med. Sci. **177**: 65-72, 1929.
376. Morton, C. B.: Peptic ulcer. IX. Chronic lesions of the duodenum following experimentally produced pyloric dysfunction, Arch. Surg. **28**: 467-478, 1934.
377. Morton, C. B.: Observations on peptic ulcer. Experiments indicating the etiologic importance of chemical and mechanical factors and their relationship to pyloric dysfunction, South. Surgeon **3**: 316-325, 1934.
378. Morton, C. B., and Graham, J. B.: Observations on peptic ulcer—VII. Clinical corroboration of experimental data, Ann. Surg. **91**: 73-78, 1930.
379. Moynihan, B.: Some problems in gastric surgery, Brit. M. J. **2**: 1021-1026, 1928.
380. Murlin, J. R.: The emptying mechanism of the stomach, J. Nutr. **2**: 311-324, 1930.
381. Necheles, H., Ling, J., and Fernando, F.: Studies on auto-digestion—I. The fate of organs implanted into the duodenum, Am. J. Physiol. **79**: 1-8, 1926.
382. Neilson, N. M., and Meyer, K. F.: The reaction and physiology of the hepatic duct and cystic bile of various laboratory animals, J. Inf. Dis. **28**: 510-541, 1921.
383. Newburger, N.: Gastric operations for benign and malignant conditions, Ann. Surg. **106**: 200-220, 1937.
384. Ochsner, A., Gage, M., and Hosoi, K.: Relationship of peptic ulceration to gastric chemism, Proc. Soc. Exp. Biol. & Med. **31**: 1260-1262, 1934.
385. Ogilvie, W. H.: The approach to gastric surgery, Lancet **2**: 295-299, 1938.
386. Okada, S.: On the reaction of bile, J. Physiol. **50**: 114-118, 1915.
387. Olch, I. Y.: Duodenal regurgitation as a factor in neutralization of gastric acidity, Arch. Surg. **16**: 125-138, 1928.
388. Oliver, J. V.: Effect of vagotomy on development of Mann-Williamson ulcer in the dog, Arch. Surg. **55**: 180-188, 1947.
389. Ophuls, W.: Gastric ulcers in rabbits following resection of the pneumogastric nerves below the diaphragm, J. Exp. Med. **8**: 181-192, 1906.
390. Orndorff, J. R., Bergh, G. S., and Ivy, A. C.: Peptic ulcer and the anxiety complex—The failure of pharmacologically sustained hypersecretion and hyperactivity of the stomach to produce chronic gastric ulcer in dogs, Surg., Gyn., & Obst. **61**: 162-166, 1935.
391. Orndorff, J. R., Fauley, G. B., and Ivy, A. C.: The prophylactic value of gastric mucin in the therapy of post-operative jejunal ulcer: an experimental study in dogs, Am. J. Dig. Dis. & Nutr. **3**: 26-34, 1936.
392. O'Shaughnessy, L.: Etiology of peptic ulcer, Lancet **220**: 177-181, 1931.
393. Owings, J. C., and Smith, J. H.: Experimental production and care of jejunal ulcers, Proc. Soc. Exp. Biol. & Med. **29**: 832-833, 1932.
394. Owings, J. C., and Smith, I. H.: The etiology of duodenal ulcers, Proc. Soc. Exp. Biol. & Med. **29**: 833-835, 1932.
395. Palmer, W. L.: Peptic ulcer and gastric secretion, Arch. Surg. **44**: 452-472, 1942.

396. Palmer, W. L.: Medical management of peptic ulcer. Symposium on gastroenterology, —Duke University, Oct. 17, 1947.
397. Pavlov, I. P.: The work of the digestive glands, Translated by W. H. Thompson, J. B. Lippincott Company, 1910.
398. Pearse, H. E., and Schilling, J. A.: Reevaluation of the role of the pyloric antrum in marginal peptic ulcers, Bull. Am. Coll. Surgeons **32**: 236, 1947.
399. Polland, W. S.: Stimulation of gastric pepsin by histamine, J. Clin. Investigation **11**: 449-454, 1932.
400. Polland, W. S., and Bloomfield, A. L.: The diagnostic value of determinations of pepsin in gastric juice, J. Clin. Investigation **9**: 107-113, 1930.
401. Poole, E. H.: (Discussion—N. Y. Surgical Soc.), Ann. Surg. **66**: 122, 1917.
402. Popielski, L.: (Quoted by Keeton and Koch) (263).
403. Porter, R. T.: Studies of the effect of atropine on gastric secretions, Proc. Soc. Exper. Biol. & Med. **29**: 504-507, 1931.
404. Portis, S. A., and Portis, B.: Effects of subtotal gastrectomy on gastric secretion, Experimental studies by aid of a Pavlov pouch in dogs, J. A. M. A. **86**: 836-839, 1926.
405. Price, P. B.: Repair in the normal and hyperacid stomach—An experimental study, Surg., Gyn., & Obst. **86**: 59-63, 1948.
406. Price, P. B., and Lee, T. F.: The gastric digestion of living tissue, Surg., Gyn., & Obst. **83**: 61-72, 1946.
407. Price, P. B., and Lee, T. F.: Digestion of living tissue by the hyperacid stomach—an experimental study, Surg., Gyn., & Obst. **84**: 959-961, 1947.
408. Priestley, J. T.: Some physiologic aspects of the surgical treatment of duodenal ulcer. S. Clin. North America **27**: 906-918, 1947.
409. Priestley, J. T., and Mann, F. C.: Gastric acidity with special reference to the pars pylorica and pyloric mucosa—an experimental study, Arch. Surg. **25**: 395-403, 1932.
410. Prohaska, J. V.: Peptic ulcer, S. Clin. North America **24**: 50-59, 1944.
411. Puestow, C. B.: The discharge of bile into the duodenum—an experimental study, Arch. Surg. **23**: 1013-1029, 1931.
412. Quigley, J. P.: Motor physiology of the stomach, the pylorus, and the duodenum, with special reference to gastro-duodenal ulcer, Arch. Surg. **44**: 414-437, 1942.
413. Ransom, H. K.: Subtotal gastrectomy for gastric ulcer—a study of end results, Ann. Surg. **126**: 633-652, 1947.
414. Reeves, T. B.: A study of the arteries supplying the stomach and duodenum and their relation to ulcer, Surg., Gyn., & Obst. **30**: 374-385, 1920.
415. Rehfuss, M. E., and Eads, J.: Motor phenomena in the gastric antrum and duodenum: Their importance in the mechanism of duodenal regurgitation, Am. J. Surg. **7**: 516-520, 1929.
416. Rienhoff, W. F.: An analysis of the results of the surgical treatment of 260 consecutive cases of chronic peptic ulcer of the duodenum, Ann. Surg. **121**: 583-599, 1945.
417. Rivers, A. B.: Clinical consideration of the etiology of peptic ulcer, Arch. Int. Med. **53**: 97-119, 1934.
418. Roberts, W. M.: Some observations on the action of belladonna and neutral fats on the acidity of the stomach contents, Quart. J. Med. **19**: 74-85, 1925.
419. Robinson, C. S.: The hydrogen ion concentration of the contents of the small intestine, J. Biol. Chem. **108**: 403-408, 1935.
420. Robinson, C. S., Luckey, H., and Mills, H.: Factors affecting the hydrogen ion concentration of the contents of the small intestine, J. Biol. Chem. **147**: 175-181, 1943.
421. Rosemann, R.: Beitrage zur Physiologie der Verdauung. I. Die Eigenschaften und die Zusammensetzung des durch Scheinfutterung gewonnen Hunde magensaftes, Pflug. Arch. ges. Physiol. **118**: 467, 1907.
422. Rosenow, E. C.: The production of ulcer of the stomach by injection of streptococci, J. A. M. A. **61**: 1947-1950, 1913.
423. Rosenow, E. C.: The causation of gastric and duodenal ulcer by streptococci, J. Infect. Dis. **19**: 332-384, 1916.
424. Roth, J. A., and Ivy, A. C.: The pathogenesis of caffeine-induced ulcers, SURGERY **17**: 644-649, 1945.
425. Roth, J. A., and Ivy, A. C.: The experimental production of acute and subacute ulcers in cats by intramuscular injection of caffeine in beeswax, Gastroenterology **2**: 274-285, 1944.
426. Roth, J. A., and Ivy, A. C.: The effect of caffeine upon gastric secretion in the dog, cat, and man, Am. J. Physiol. **141**: 454-461, 1944.
427. Roth, J. A., Ivy, A. C., and Atkinson, A. J.: Caffeine and peptic ulcer—Relation of caffeine and caffeine containing beverages to the pathogenesis, diagnosis and management of peptic ulcer, J. A. M. A. **126**: 814-819, 1944.
427a. Ruffin, J. M., and White, D. P., Jr.: The present status of vagotomy in the treatment of peptic ulcer, Gastroenterology **10**: 607-615, 1948.

428. Ruffin, J. M., Grimson, K. S., and Smith, R. C.: The effect of transthoracic vagotomy upon the clinical course of patients with peptic ulcer, Gastroenterology **7**: 599-606, 1946.

428a. Ruggiero, W. F., Cotvi, F., and Bianco, A.: The management of ambulatory peptic ulcer patients with protein hydrolysates, New York State J. Med. **46**: 2395-2398, 1946.

429. Sacks, J., Ivy, A. C., Burgess, J. P., and Vandolah, J. E.: Histamine as the hormone for gastric secretion, Am. J. Physiol. **101**: 331-338, 1932.

430. St. John, F. B., Flood, C. A., and Guis, J. A.: Effect of partial gastrectomy on acidity and peptic activity of gastric juice, Surgery **5**: 179-185, 1939.

431. St. John, F. B., Whipple, A. O., and Raiford, T. S.: Treatment of carcinoma of the stomach—summary of results, Am. J. Surg. **31**: 246, 1936.

432. Saltzstein, H. C., and Kurtz, I. J.: The effects of pedicle jejunal transplants in the stomachs of Mann-Williamson dogs, Surg., Gyn., & Obst. **82**: 194-198, 1946.

433. Saltzstein, H. C., Sandweiss, D. J., Hammer, J. M., Hill, E. J., and Vandenberg, H. J.: Effect of enterogastrone on Mann-Williamson ulcers in dogs, Arch. Surg. **55**: 125-129, 1947.

434. Saltzstein, H. C., Sandweiss, D. J., Hammer, J. M., Hill, E. J., and Vandenberg, H. J.: Effect of vagotomy on Mann-Williamson ulcers in dogs, Arch. Surg. **55**: 130-140, 1947.

435. Sandblom, P., Bergh, G. S., and Ivy, A. C.: Cholecystoduodenostomy combined with pyloric exclusion, Ann. Surg. **104**: 702-711, 1936.

436. Sanders, R. L.: A review of 101 subtotal gastrectomies for benign ulcer, Surgery **18**: 229-237, 1945.

437. Sandweiss, D. J., Saltzstein, H. C., and Glazer, W. S.: The value of histidine in prevention of experimental ulcer in dogs, Am. J. Dig. Dis. & Nutr. **4**: 20-23, 1937.

438. Sandweiss, D. J., Sugarman, M. H, and Podolsky, H. M.: Nocturnal gastric secretion in duodenal ulcer—Studies on normal subjects and patients with their bearing on ulcer management, J. A. M. A. **130**: 258-265, 1946.

439. Saunders, E. W.: The serologic and etiologic specificity of the alpha streptococcus of gastric ulcer—a bacteriologic study, Arch. Int. Med. **45**: 347-382, 1930.

440. Schiffrin, M. J., and Ivy, A. C.: Physiology of gastric secretion, particularly as related to the ulcer problem, Arch. Surg. **44**: 399-413, 1942.

441. Schiffrin, M. J., and Warren, A. A.: Some factors concerned in the production of experimental ulceration of the gastro-intestinal tract in cats, Am. J. Dig. Dis. **9**: 205-209, 1942.

442. Schindler, R., and Dailey, M. E.: Gastroscopic observations on gastric motility, Am. J. Dig. Dis. **8**: 8-10, 1941.

443. Schmilinsky, H.: Die Einleitung der gesamten Duodenalsafte in den Magen (innere Apotheke), Zentralbl. f. Chir. **45**: 416-418, 1918.

444. Scott, G. H.: The growth in surface area of the human gastric mucosa, Anat. Record **43**: 131-144, 1929.

445. Scott, W. J. M.: The relationship of non-absorbable suture material to jejunal ulcer—An experimental study, Arch. Surg. **18**: 1584-1593, 1929.

446. Scott, V. B., Graham, J. S., and McCartney, D. H.: Exocrine pancreatic secretion in the fasting dog, Am. J. Dig. Dis. **7**: 533-537, 1940.

447. Seely, H., and Zollinger, R.: Fundusectomy in the treatment of peptic ulcer—An experimental study, Surg., Gyn., and Obst. **61**: 155-161, 1935.

448. Selinger, J.: Peptic ulcer in infants under one year of age. Ann. Surg. **96**: 204-209, 1932.

449. Shapiro, P. F., and Berg, B. N.: Return of gastric acidity after subtotal gastrectomy and double vagotomy, Arch. Surg. **28**: 160-179, 1934.

450. Shapiro, P. F., and Ivy, A. C.: Gastric ulcer—IV. Experimental production of gastric ulcer by local anaphylaxis, Arch. Int. Med. **38**: 237-258, 1926.

451. Shay, H., and Gershon-Cohen, J.: Experimental studies in gastric physiology in man. II. A study of pyloric control. The roles of acids and alkalis, Surg., Gyn., & Obst. **58**: 935-955, 1934.

452. Shay, H., and Gershon-Cohen, J.: Experimental studies in gastric physiology in man: The mechanism of gastric evacuation after partial gastrectomy as demonstrated roentgenologically, Am. J. Dig. Dis. & Nutr. **2**: 608-612, 1936.

453. Shay, H., Gershon-Cohen, J., and Fels, S. S.: A self-regulatory duodenal mechanism for gastric acid control and an explanation for the pathologic gastric physiology in uncomplicated duodenal ulcer, Am. J. Dig. Dis. **9**: 124-128, 1942.

454. Shay, H., Katz, A. B., and Schloss, E. M.: Experimental studies in gastric physiology. Evaluation of the role of duodenal regurgitation in the control of gastric acidity in man (Boldyreff theory), Arch. Int. Med. **50**: 605-620, 1932.

455. Shay, H., Komarov, S. A., Fels, S. S., Meranze, D., Gruenstein, M., and Siplet, H.: A simple method for the uniform production of gastric ulceration in the rat, Gastroenterology **5**: 43-61, 1945.

456. Small J. T.: Denervation of the stomach, Arch. Surg. 55: 189-204, 1947.
457. Smith, G. M.: An experimental study of the relation of bile to ulceration of the mucous membrane of the stomach, J. Med. Research 30: 147-184, 1914.
458. Smith, D. T., and McConkey, M.: Peptic ulcer (gastric, pyloric, and duodenal)—Occurrence in guinea pigs fed on a diet deficient in vitamin C, Arch. Int. Med. 51: 413-427, 1933.
459. Somervell, T. H.: Physiological gastrectomy: The operation of ligature of the arteries of the stomach to relieve hyperacidity and to prevent recurrent ulceration after gastroenterostomy, Brit. J. Surg. 33: 146-152, 1945.
460. Spencer, W. H., Meyer, G. P., Rehfuss, M. E., and Hawk, P. B.: Gastrointestinal studies. XII. Direct evidence of duodenal regurgitation and its influence upon the chemistry and function of the normal human stomach, Am. J. Physiol. 39: 459-479, 1915.
461. Stalker, L. K., Bollman, J. L., and Mann, F. C.: Experimental peptic ulcers produced by cincophen, Proc. Staff Meet. Mayo Clin., 11: 695-699, 1936.
462. Starlinger, F.: Das Rückfallsgeschwür nach Magenresektion wegen Ulcus ventriculi oder duodeni, Arch. f. klin. Chir. 162: 564, 1930.
463. Stefko, P., Andrus, W. D., and Lord, J. W.: The effects of jejunal transplants on gastric acidity, Science 96: 208-209, 1942.
464. Stein, I. F., Grossman, M. I., and Ivy, A. C.: Experimental production of ulcers in closed gastric pouches in dogs, SURGERY 22: 552-557, 1947.
465. Steinberg, M. E.: The surgical treatment of gastroduodenal ulcerations. The technique of gastric resection, Surg., Gyn., & Obst. 71: 317-333, 1940.
466. Steinberg, M. E., Brougher, J. C., and Vidgoff, I. J.: Changes in the chemistry of the contents of the stomach following gastric operations, Arch. Surg. 15: 749-761, 1927.
467. Steinberg, M. E., and Proffitt, J. C.: The etiology of postoperative peptic ulcers, Arch. Surg. 25: 819-848, 1932.
468. Steinberg, M. E., and Starr, P. H.: The factor of spasm in the etiology of peptic ulcers, Arch. Surg. 29: 895-906, 1934.
469. Stevens, G. A.: The capacity of the duodenum to neutralize, buffer and to dilute acid, Am. J. Dig. Dis. & Nutr. 2: 288-293, 1935.
470. Stevens, R. E., Segal, H. L., and Scott, W. J. M.: The effect upon gastric secretion of introducing dilute hydrochloric acid into the duodenum. A study of normal humans and duodenal ulcer patients, Am. J. Dig. Dis. 6: 706-711, 1940.
471. Still, E. V., McBean, J. W., and Ries, F. A.: Studies on the physiology of secretin. IV. The effect on the secretion of bile, Am. J. Physiol. 99: 94-100, 1931.
472. Strauss, A. A., Bloch, L., and Friedman, J. G.: Gastrojejunal ulcer—medical and surgical considerations, J. A. M. A. 90: 181-186, 1928.
473. Strauss, A. A., Strauss, S., Levitsky, P., Scheman, L., Seidmon, E. E., Arens, R. A., Meyer, J., and Necheles, H.: Physiological and clinical study of patients after subtotal gastrectomy, Am. J. Dig. Dis. & Nutr. 4: 32-37, 1937.
474. Thomas, J. E.: Some physical and physiological factors involved in the regulation of gastric emptying, Rev. Gastroenterol. 2: 32-38, 1935.
475. Thomas, J. E.: The maximal acidity of the intestinal contents during digestion, Am. J. Dig. Dis. 7: 195-197, 1940.
476. Thomas, J. E., Crider, J. O., and Morgan, C. J.: A study of reflexes involving the pyloric sphincter and antrum and their role in gastric evacuation, Am. J. Physiol. 108: 683-699, 1934.
477. Thompson, H. L., and Prout, H.: Surgical treatment of peptic ulcer—Recent experience of Los Angeles General Hospital, Arch. Surg. 54: 390-413, 1947.
478. Thornton, T. F., Storer, E. H., and Dragstedt, L. R.: Supradiaphragmatic section of the vagus nerves—Effect on gastric secretion and motility in patients with peptic ulcer, J. A. M. A. 130: 764-769, 1946.
479. Toby, C. G.: Does histamine stimulate the secretory activity of the peptic cells in man? Am. J. Dig. Dis. & Nutr. 3: 902-903, 1937.
480. Tomoda, M., and Aramaki, J.: Ueber die Magensaftacidität nach Operationen wegen Magen-Duodenalgeschwür, unter Berücksichtigung der Beziehung zwischen dem Operationserfolg und dem postoperativen Magensaftbefund, Arch. f. clin. Chir. 192: 604-617, 1938.
481. Trach, B., Code, C. F., and Wangensteen, O. H.: Histamine in human gastric mucosa, Am. J. Physiol. 141: 78-82, 1944.
482. Truesdale, P. E.: The pylorus: Observations upon its musculature, Surg., Gyn. & Obst. 21: 298-303, 1915.
483. Turck, F. B.: Ulcer of the stomach: Pathogenesis and pathology. Experiments in producing artificial gastric ulcer and genuine induced peptic ulcer, J. A. M. A. 46: 1753-1763, 1906.
484. Underhill, F. P., and Freiheit, J. M.: Effect of pilocarpine and epinephrine in the production of specific lesions in the stomach of rabbits, Arch. Path. 5: 411-428, 1928.

485. Vale, C. F.: Gastric resection for ulcer—experience in forty-four cases, Am. J. Surg. **55**: 500-503, 1942.
486. Van Wagoner, F. H., and Churchill, T. P.: Production of gastric and duodenal ulcers in experimental cincophen poisoning, J. A. M. A. **99**: 1859-1860, 1932.
487. Vanzant, F. R.: Late effects of section of the vagus nerves on gastric acidity, Am. J. Physiol. **99**: 375-378, 1931.
488. Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L., and Berkson, J.: The normal range of gastric acidity from youth to old age—the analysis of 3,746 records, Arch. Int. Med. **49**: 345-359, 1932.
489. Vanzant, F. R., Osterberg, A. E., Alvarez, W. C., and Rivers, A. B.: Studies of pepsin in human gastric juice. IV. The influence of gastric and duodenal disease, Am. J. Dig. Dis. & Nutr. **3**: 97-100, 1936.
490. Varco, R. L., Code, C. F., Walpole, S. H., and Wangensteen, O. H.: Duodenal ulcer formation in the dog by intramuscular injections of a histamine beeswax mixture, Am. J. Physiol. **133**: 475-476, 1941.
491. Vineberg, A. M.: The activation of different elements of the gastric secretion by variation of vagal stimuli, Am. J. Physiol. **96**: 363-369, 1931.
492. Vineberg, A. M., and Babkin, B. P.: Histamine and pilocarpin in relation to the gastric secretion, Am. J. Physiol. **97**: 69-73, 1931.
493. Vitkin, S. F.: Motor functions of the stomach after resection, Ann. Surg. **111**: 27-48, 1940.
494. Walpole, H., Varco, R. L., Code, C. F., and Wangensteen, O. H.: Production of gastric and duodenal ulcers in the cat by intramuscular implantation of histamine, Proc. Soc. Exper. Biol. & Med. **44**: 619-621, 1940.
495. Walters, W.: The choice of surgical procedures for duodenal ulcer, Ann. Surg. **96**: 258-268, 1932.
496. Walters, W.: Gastric acidity following operations for gastric and duodenal ulcer. Its effect on the question of partial gastrectomy, Ann. Surg. **104**: 585-593, 1936.
497. Walters, W.: Should gastric resection be done for duodenal ulcer? Surgery **2**: 759-768, 1937.
498. Walters, W., Lewis, E. B., and Lemon, R. G.: Primary partial gastrectomy (Polya type) for duodenal ulcer—a study of results in 212 cases, Surg., Gyn., & Obst. **71**: 240-243, 1940.
499. Walters, W., Neibling, H. A., Bradley, W. F., Small, J. T., and Wilson, J. W.: Gastric neurectomy-anatomic and physiologic studies with favorable and unfavorable results in the treatment of peptic ulcer, Arch. Surg. **55**: 151-163, 1947.
500. Walton, A. J.: Gastrojejunal ulcer, Lancet **2**: 800-804, 1925.
501. Walton, A. J.: Gastrojejunal ulceration, Brit. J. Surg. **22**: 33-55, 1934.
502. Wangensteen, O. H.: The problem of surgical arrest of massive hemorrhage in duodenal ulcer, SURGERY **8**: 275, 1940.
503. Wangensteen, O. H.: The surgeon and the ulcer problem, Illinois M. J. **80**: 100-110, Aug., 1941.
504. Wangensteen, O. H.: Method of closing the pyloro-antral pouch in the antral exclusion operation, SURGERY **12**: 731-741, 1942.
505. Wangensteen, O. H.: The surgical management of ulcer—A chemical problem, Proc. Interst. Post grad. M. A. N. A. **70**: 178, 1942.
506. Wangensteen, O. H.: Clinical aspects of the ulcer problem, Minnesota Med. **27**: 714-722, 1944.
507. Wangensteen, O. H.: Causes of failure after gastric resection for ulcer, Wisconsin M. J. **44**: 878-888, 1945.
508. Wangensteen, O. H.: The ulcer problem. (Seventh Listerian Oration), Canad. M. A. J. **53**: 309, 1945.
509. Wangensteen, O. H.: Studies in etiology and surgical management of ulcer, Symposium on gastroenterology—Duke University, Oct. 17, 1947.
510. Wangensteen, O. H., and Lannin, B.: Criteria of an acceptable operation for ulcer—The importance of the acid factor, Arch. Surg. **44**: 489-500, 1942.
511. Wangensteen, O. H., Merendino, A., and Litow, S. S.: Hematemesis from erosion or ulcer (Gastric and/or duodenal), An occasional complication of fracture, Bull. Am. Coll. Surg. **30**: 58, 1945.
512. Wangensteen, O. H., Varco, R. L., Hay, L. J., Walpole, S. W., and Trach, B. H.: Gastric acidity before and after operative procedure with special reference to the role of the pylorus and antrum, Ann. Surg. **112**: 626-670, 1940.
513. Warren, R.: Experiences with vagectomy for peptic ulcer with report of an unsuccessful case, SURGERY **22**: 246-258, 1947.
514. Watson, J. R.: Effect of fundusectomy on the acidity of the gastric and duodenal content—an experimental study, Arch. Surg. **31**: 1-9, 1935.

515. Watts, S. H.: A case of peptic ulcer in the jejunum of a dog following gastroenterostomy with a review of the cases reported in man, Johns Hopkins Hosp. Bull. **14:** 191-193, 1903.
516. Weech, A. A., and Paige, B. H.: Nutritional edema in the dog. IV. Peptic ulcer produced by the same low protein diet that lends to hypoproteinemia and edema, Am. J. Path. **13:** 249-256, 1937.
517. Weeks, C., Ryan, B. J., and VanHoy, J. M.: Two deaths associated with supradiaphragmatic vagotomy, J. A. M. A. **132:** 988-990, 1946.
518. Weir, J. F.: Phenomena including recurrent ulcer following resection of benign lesions, Am. J. Surg. **7:** 505-515, 1929.
519. Weiss, A. G., and Aron, E: Role desacides amines dans l'evolution de l'ulcere experimental. Influence de l'histidine, La Presse Medicale **41:** 1880-1883, 1933.
520. Weiss, A. G., Graves, A., and Gurriaran, G.: La derivation intragastrique des sucs alcalins duodenaux, C. Rend. Soc. Biol. **109:** 916-920, 1932.
521. Weiss, A. G., and Gurriaran, G.: Sur une methode permettant d'obtenir des ulceres gastro-duodeneaux experimentaux, C. Rend. Soc. Biol. **102:** 48-50, 1929.
522. Weiss, A. G., and Hubster, C.: The pathogenesis of gastroduodenal ulcer, Internat. Abst. Surg. **52:** 22-23, 1931.
523. Werle, J. M., Brody, D. A., Ligon, E. W., Read, M. R., and Quigley, J. P.: The mechanics of gastric evacuation, Am. J. Physiol. **131:** 606-614, 1941.
524. Wilensky, A. D., and Geist, S. H.: Experimental studies in the production of chronic gastric ulcer, J. A. M. A. **66:** 1382, 1916.
525. Wilhelmj. C. M., and Finegan, R. W.: The gastric secretory curve before and after the Mann-Williamson operation, and its bearing on the normal regulation of gastric acidity, Am. J. Dig. Dis. **5:** 373-377, 1938.
526. Wilhelmj. C. M., Finegan, R. W., and Hill, F. C.: The physiological control of gastric acidity, Am. J. Dig. Dis. & Nutr. **4:** 547-550, 1938.
527. Wilhelmj, C. M., McCarthy, H. H., and Hill, F. C.: Acid inhibition of the intestinal and intragastric chemical phases of gastric secretion, Am. J. Physiol. **118:** 766-774, 1937.
528. Wilhelmj, C. M., O'Brien, F. T., and Hill, F. C.: The influence of the pylorus on the secretion of acid by the fundus, Am. J. Physiol. **116:** 685-696, 1936.
529. Wilhelmj, C. M., O'Brien, F. T., McCarthy, H. H., and Hill, F. C.: The role of the duodenal secretions in the prevention of experimental jejunal ulcer, Am. J. Physiol. **117:** 79-85, 1936.
530. Wilkie, D. P. D.: Jejunal ulcer—some observations on its complications and their treatment, Ann. Surg. **99:** 401-409, 1934.
531. Winkelbauer, A., and Starlinger, F.: Experimentelles zur Pathogenese des Ulcus pepticum jejuni postoperativum, Arch. f. klin. Chir. **140:** 460-482, 1928.
532. Winkelstein, A.: One hundred and sixty-nine studies in gastric secretion during the night, Am. J. Dig. Dis. & Nutr. **1:** 778-782, 1935.
533. Winkelstein, A., and Berg, A. A.: Vagotomy plus partial gastrectomy for duodenal ulcer, Am. J. Dig. Dis. **5:** 497-501, 1938.
534. Wolf, S., and Wolff, H. G.: Human gastric function—An experimental study of a man and his stomach, Oxford University Press, 1943.
535. Wolfer, J. A.: Chronic ulcer of the stomach: its experimental production and effect on gastric secretion and motility, Ann. Surg. **84:** 89-94, 1926.
536. Wolfson, W. L., and Rothenberg, R. E.: The surgical treatment of complicated duodenal ulcer, SURGERY **3:** 663-669, 1938.
537. Wright, G.: Collective inquiry by the Fellows of the Association of Surgeons into gastro-jejunal ulceration, Brit. J. Surg. **22:** 433-455, 1935.
538. Wu, P. P. T.: Reactions of contents of jejunum and experimental production of peptic ulcer, Arch. Surg. **30:** 557-562, 1935.
539. Wu, P. P. T.: The effect of histidine on the experimental production of peptic ulcer, Ann. Surg. **106:** 196-199, 1937.
540. Yesko, S. A.: The effects of ligation of pancreatic ducts on gastric digestion, Am. J. Physiol. **86:** 483-489, 1928.
541. Zollinger, R.: The surgical treatment of gastric and duodenal ulcer, Surgery **7:** 427-452, 1940.